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Scancell Holdings

New frontiers in T-cell activation and targeting

Scancell is a clinical stage pharmaceutical company developing two distinct flexible cancer immunotherapy platforms, each with broad applications. ImmunoBody is a DNA vaccine which stimulates high avidity anti-tumour T-cells for use as a monotherapy or in combination with checkpoint inhibitors. Moditope targets modified antigens and stimulates powerful anti-tumour T-cell responses for use in advanced and hard-to-treat cancers. Both platforms are targeting multi-billion dollar markets. The recent capital increase will be used to advance both platforms to the next stage of development and investment in corporate infrastructure.

- **Strategy**: Scancell is developing two proprietary immuno-oncology platforms which target cancer cells directly to produce potent T-cell responses. Both technologies are highly flexible, potentially targeting many types of cancer. The initial aim is to complete proof-of concept trials in five different indications.

- **ImmunoBody:** DNA-based platform administered using electroporation. It is the only DNA platform that utilises both cross- and direct-presentation. This dual mechanism provides a 100-fold increase in T-cell avidity. Phase II trials in combination with checkpoint inhibitors are scheduled for 2017.

- **Moditope:** Peptide-based immunotherapy platform that targets neo-epitopes in the stressed cellular environment generated during cancer development. It induces potent inflammatory T-cell responses, a new approach that works independently of checkpoint inhibitors for treatment of advanced cancers.

- **Risks:** Scancell is an early-stage drug development company which carries a high risk that a product might fail in clinical trials. Its activity focus on cancer immunotherapy is an extremely exciting, but competitive, field. More capital will be required to advance its proprietary assets further along the value chain.

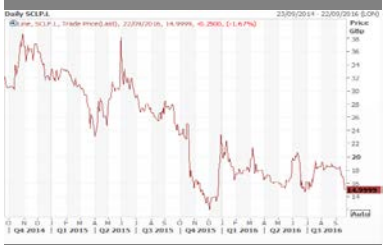
- **Investment summary:** Scancell is trading on an EV of £33m, compared to a cumulative investment of £19m to get the company where it is today, which is low compared to its relevant peers. Scancell's proprietary technologies are in the 'hot' area of immuno-oncology and targeting markets of significant unmet medical need. Given that big pharma is willing to pay handsomely for such validated assets, we foresee considerable upside potential in the shares.

Financial summary and valuation

Year end Apr (£m)	2014	2015	2016	2017E	2018E	2019E
Sales	0.00	0.00	0.00	0.0	0.0	0.0
R&D investment	-1.68	-2.00	-1.85	-3.6	-6.0	-9.7
Underlying EBIT	-2.45	-2.87	-3.00	-6.0	-8.6	-12.5
Reported EBIT	-2.50	-2.96	-3.04	-6.0	-8.6	-12.6
Underlying PBT	-2.42	-2.74	-2.99	-6.0	-8.5	-12.5
Statutory PBT	-2.47	-2.83	-3.03	-6.0	-8.5	-12.5
Underlying EPS (p)	-1.00	-1.03	-1.08	-2.0	-1.8	-2.6
Statutory EPS (p)	-1.03	-1.07	-1.10	-2.0	-1.8	-2.6
Net (debt)/cash	5.57	3.06	6.53	22.7	15.0	3.7
Capital increase	6.16	0.00	5.79	21.7	0.0	0.0
P/E (x)	-	-	-	-	-	-
EV/sales (x)	-	-	-	-	-	-

Source: Hardman & Co Life Sciences Research

Pharmaceuticals & Biotech



Source: Eikon Thomson Reuters

Market data

EPIC/TKR	SCLP
Price (p)	15.0
12m High (p)	26.0
12m Low (p)	12.0
Shares (m)	261.8
Mkt Cap (£m)	39.2
EV (£m)	32.7
Free Float*	75%
Market	AIM

**As defined by AIM Rule 26*

Description

Scancell is a clinical-stage company focused on the discovery and development of two proprietary immunotherapy platforms with the potential to be used as therapeutic cancer vaccines.

Company information

Exec Chairman	John Chiplin
CEO	Richard Goodfellow
CSO	Prof. Lindy Durrant
US Office	+1 858 900 2646
UK HQ	+44 1865 338 069
	www.scancell.co.uk

Key shareholders

Directors	6.6%
Calculus Capital	18.5%
Share Nominees	8.5%
Hargreaves Lansdown	7.2%
Barclayshare Nominees	5.7%
Lynchwood Nominees	4.8%

Next event

16 Sept	Finals
Oct-16	AGM
Jan-17	Interims

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Executive summary

Background

Two distinct proprietary immuno-therapy platforms…

…ImmunoBody and Moditope

Scancell Holdings is a clinical stage pharmaceutical company that is developing in parallel two distinct cancer immunotherapy platforms – ImmunoBody and Moditope – which employ different approaches to trigger cancer specific immune responses. The ImmunoBody DNA plasmid platform stimulates a potent anti-tumour response *via* a dual mode of action triggering high avidity killer T-cells. Moditope uses the novel concept that stressed cells, including cancer, activate enzymes to modify amino acids to alert the immune response. An initial proof-of-concept trial with Scancell's lead ImmunoBody candidate, SCIB1, in malignant melanoma has produced exceptional clinical outcomes in patients with Stage III/IV resected disease, with 19/20 patients remaining alive with a median observation time of 49 months (2-4mg dose group). Strong science is at the heart of Scancell, which raised capital earlier in 2016 to prepare the groundwork for taking both platforms to the next stage of clinical development.

ImmunoBody platform

ImmunoBody produces the high avidity T-cell responses essential for tumour killing…

In contrast to traditional immunisation, the ImmunoBody platform has a dual mode of action – namely direct- and cross-presentation – to produce high avidity $CD8^+$ T-cell responses that can kill tumour cells. The potency of these responses differentiates ImmunoBody from other vaccines which frequently induce only low avidity T cell responses which fail to kill tumour cells.

The specificity of ImmunoBody is enhanced *via* this synergistic dual mechanism of action:

- **Direct presentation** – DNA plasmids transfect directly antigen presenting cells (APCs) which process the ImmunoBody and present the encoded epitopes *via* MHC molecules to T-cells, and
- **Cross presentation amplification pathway** – DNA plasmids transfect non-APCs which, in turn, synthesise and secrete the engineered ImmunoBody antibody which then targets CD64 on activated APCs

…via its unique synergistic dual mechanism of action…

…that enhances the response 100-fold

The combination of these approaches produces a synergistic 100-fold enhancement in T-cell avidity which is vital for tumour cell death. ImmunoBody is the only platform with this dual mechanism of action. Conventional DNA vaccination or protein/peptide immunisation triggers only low avidity immune responses via a single induction pathway. Whereas Scancell's ImmunoBody approach activates T-cell responses through both these distinct pathways: (1) direct presentation of the plasmid to the cell and (2) cross presentation amplification pathway, which is unique to the ImmunoBody platform. Therefore, ImmunoBody is a powerful DNA-based immunotherapy platform for generation of ultra-high avidity anti-tumour T-cell responses.

In addition, the ImmunoBody platform works following a simple injection into a healthy muscle, whereas alternative technologies, such as Provenge (Dendreon), require a patient's dendritic cells to be harvested, mixed with the antigens and then re-injected back into the patient, which is time-consuming and expensive.

Validated in a proof-of concept trial in melanoma that produced unprecedented survival outcomes

ImmunoBody has been validated *in vivo* both pre-clinically and clinically. In an ongoing proof-of-concept clinical trial with SCIB1 in melanoma patients that started in 2010, low toxicity and survival well beyond the accepted norm has been demonstrated. Following the initial proof-of-concept trial with SCIB1, Scancell plans to start a Phase IIb trial in combination with a checkpoint inhibitor in 3Q 2017.

In contrast to cellular approaches such as chimeric antigen receptor transduced T-cells (CAR-T-cells) which are patient specific costly and time consuming to manufacture, Immunobody is rapid, inexpensive and applicable to a wide range of patients. Different T-cell epitopes can be grafted into the engineered ImmunoBody antibody framework allowing rapid customisation for different tumour types to produce a pipeline of therapeutic vaccines.

ImmunoBody platform – Lead candidates

ImmunoBody	SCIB1	SCIB2
Indication	Melanoma	Non-small cell lung cancer
Stage	Phase I/II	Pre-clinical
Description	SCIB1 encodes two CD8 epitopes from melanoma antigens TRP-2 and gp100 plus two CD4 epitopes from gp100	SCIB2 encodes sixteen NY-ESO-1 T-cell epitopes

Source: Scancell, Hardman & Co Life Sciences Research

Moditope platform

The Moditope platform utilises 'stressed' conditions generated by tumours

Moditope is the first vaccine type to target amino acid modifications produced by enzymes induced by cellular stress to alert an immune response. By their very nature, cancer cells are rapidly dividing and therefore require a plentiful supply of nutrients to proliferate and survive, creating a 'stressed' environment. Scancell is the first company in the world to show that tumour cells activate these enzymes and express these modified neo-epitopes which are excellent targets for vaccine therapy. Moditope is a modified peptide-based immunotherapy that induces potent inflammatory T-helper cell responses that overcome the immunosuppressive environment and kill cancer cells.

Cancer cells promote autophagy to enable their self-preservation

One of the tools used by cancer cells to promote their survival in this stressed situation is a mechanism termed autophagy, which digests internal organelles and proteins to supply vital nutrients. Enzymes that convert arginine to citrulline are also activated within autophagosomes and modify peptides to present to the immune response to warn it of the cells stress. Scancell's discovery illustrates for the first time how citrullinated peptides produced during autophagy have become a novel target for cancer therapy and is the basis of Scancell patent filings from 2012.

The citrullination mechanism has also been shown to be involved in the pathogenesis of autoimmune disease. However, as this is mediated by an antibody response rather than a T-cell response, the potential of inducing autoimmune side effects with Moditope is thought to be low.

The discovery of citrullination is fundamental to Moditope's action…

Scancell's lead candidate using the Moditope platform is Modi-1, a therapeutic peptide vaccine which contains a combination of two citrullinated vimentin epitopes and one citrullinated α-enolase epitope. It is expected to enter proof-of-concept trials in advanced osteosarcoma, triple negative breast cancer and ovarian cancer in 2018.

…and altering target epitopes results in different products

The Moditope platform is also very flexible. Many proteins are citrullinated in a stressed environment and the possibility of changing the target epitopes results in different products which could be used to treat different types of cancer.

Comparison of Scancell platform technologies	
ImmunoBody	**Moditope**
DNA-based transcribes a CD64 targeting antibody	Peptide-based
High avidity $CD8^+$ T-cell responses	Potent $CD4^+$ T-cell responses
For use in small, primary and metastatic tumours as monotherapy	For use in advanced/bulky tumours
Powerful synergistic effect with checkpoint inhibitors for late-stage disease	No requirement for checkpoint inhibitors
Potent killer cells induced	Reverses immunosuppressive tumour environment
Targets tumour-associated antigens	Targets modified self-antigens
Can easily be adapted to target other cancers	Possibility of targeting a vast spectrum of cancers

Source: Scancell, Hardman & Co Life Sciences Research

Complementary technologies

Scancell's two platforms are complementary

Although both of Scancell's platforms produce T-cell responses, they are considered to be complementary platforms that do not compete with each other:

- ImmunoBody is suitable for use as monotherapy for early-stage cancers in order to eliminate micro-metastases, but also as combination therapy with a checkpoint inhibitor for late-stage disease
- Moditope is targeting late-stage and hard-to-treat cancers when cells are particularly stressed. Because it targets the CD4 killer T-helper cell response, it may not require concomitant use with a checkpoint inhibitor

R&D pipeline

Scancell's pipeline consists of three products and one line-extension

Scancell's pipeline is comprised of three products and one line-extension targeting five cancers with unmet need. The ImmunoBody platform has generated SCIB1 and SCIB1 PLUS for malignant melanoma, and SCIB2 for non-small cell lung cancer (NSCLC). Modi-1, which is derived from the Moditope platform, will target triple negative breast cancer, ovarian cancer and osteosarcoma and is expected to enter clinical trials in 2018.

Scancell – R&D pipeline

Platform	Product candidate	Indication	Pre-clinical	Phase I	Phase II	Phase III	Approved
ImmunoBody	SCIB1	Melanoma	→	→	→		
	SCIB2	Non-small cell lung cancer	→				
	SCIB1 PLUS	Melanoma	→				
Moditope	Modi-1	Triple –ve breast cancer Ovarian cancer Osteosarcoma	→				

Source: Hardman & Co Life Sciences Research

In 3Q 2017, Scancell will initiate a Phase IIb study in combination with a checkpoint inhibitor

In Phase I/IIa proof-of-concept trials in malignant melanoma, SCIB1 has achieved unprecedented survival rates in 20 melanoma Stage III/IV patients with resected melanoma, was well tolerated, thereby validating the ImmunoBody technology in a clinical setting. In 3Q 2017, Scancell will initiate a Phase IIb trial with SCIB1 in combination with a checkpoint inhibitor (Keytruda or Opdivo). With positive outcomes, management will look to out-license this asset for late-stage development and commercialisation for melanoma.

Newsflow

Combination results are due by the end of 2018

Having ascertained that the initial clinical trial supplies of SCIB1 were no longer within specification after seven years, Scancell moved quickly to identify and sign up a specialist GMP manufacturer – Eurogentec SA – to produce a new batch of SCIB1 for use in the on-going Phase I/II trial, and the combination trial with a checkpoint inhibitor. Headline data are expected to be released towards the end of 2018.

Modi-1 trial results are likely towards the end of 2019

Modi-1, the lead candidate from the Moditope platform, is expected to commence a Phase I clinical proof-of-concept monotherapy trial in triple negative breast cancer, osteosarcoma and ovarian cancer in 2018, with headline results likely towards the end of 2019.

Scancell – Development timetable

Product candidate	Indication	2016	2017	2018	2019
SCIB1	Melanoma	GMP manufacture, IND		Ph II in combination with PD-1	
SCIB2	Non-small cell lung cancer	Cell banks, Feasibility	GMP manufacture, Toxicology	Ph I/II in combination with PD-1	
SCIB1 PLUS	Melanoma				
Modi-1	Triple –ve breast cancer Ovarian cancer Osteosarcoma		Feasibility, GMP manufacture, Toxicology	Ph I/II	

Source: Hardman & Co Life Sciences Research

Commercial opportunity

Scancell is operating in a very competitive environment. However, despite all the research and commercialisation of new drugs, there is still a desperate need for new effective cancer drugs associated with low toxicity. Therefore, the fact that Scancell has two novel complimentary and proprietary platforms indicates that the company is well positioned in this complex field.

Hardman estimated the cancer drug market to be $105bn in 2015…

…with potential to rise to >$250bn in 2020

Based on ex-factory sales of 110 branded cancer drugs, Hardman & Co estimates that underlying growth in the global oncology market was +8-9% in 2015, worth $104.5bn. Over the last 10 years, the global oncology market showed +9.0% CAGR. Over this period, the market was driven by sales of immunotherapy drugs led by the antibodies, which represented an estimated 27% of the market in 2015. Given the scale of current development programmes, Hardman & Co expects the historic growth rate of +8-9% compound to be maintained for the foreseeable future and is forecasting that the oncology market will grow to $154-161bn in 2020.

Each of Scancell's platforms represents a multi-billion dollar opportunity

With its two differentiated platforms that can be applied to many types of cancer, Scancell's products will become part of the overall immunotherapy segment of the market which is clearly a multi-billion dollar opportunity.

Corporate developments

Investment also in corporate infrastructure…

Following the capital increase in April to fund the feasibility, GMP manufacture and regulatory liaison work for the proposed clinical trial programme, Scancell has also made some corporate changes. The company has opened a new US office in San Diego from where all its US clinical trial activities will be co-ordinated. The office will be headed up by John Chiplin who has become Executive Chairman.

…to support a growing company

In addition, the joint CEO role has been split, with Dr Richard Goodfellow becoming sole CEO and Professor Lindy Durrant assuming the role of Chief Scientific Officer. Scancell has also opened an office in Oxford to co-ordinate all product development and the European arm of the clinical trials.

Valuation

These flexible assets addressing a 'hot' area will be attractive to big pharma

Scancell's proprietary technologies are in the 'hot' area of immuno-oncology, targeting markets of significant unmet medical need. Most products that have achieved a successful regulatory outcome and been commercialised have all seen rapid uptake, generating strong sales, which suggests that these flexible assets will be very attractive to big pharma and or biotech companies.

Anew entrant would need to spend considerably more to get into the same proprietary position as Scancell

Scancell is trading on an enterprise value of £33m compared to a cumulative investment of £19m to get the company where it is today. Is this a fair reflection of the company's achievements? Certainly, another company starting out fresh today would need to spend considerably more than this to get to the same position as Scancell with two proprietary immunotherapy platforms.

Comparative valuation

Inovio is a good comparator…

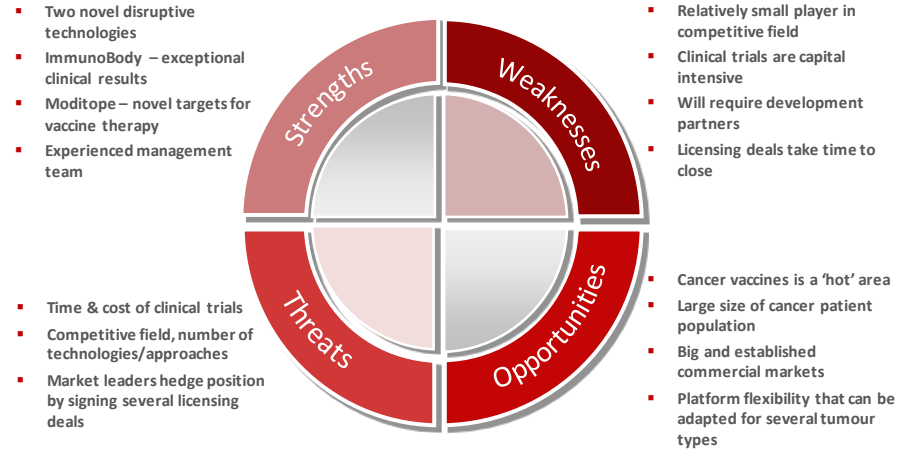
…but its main IP surrounds the administration platform…

…rather than the immunotherapy platforms of Scancell

Inovio Pharmaceuticals (INO.OQ) is a company that competes in the same field as Scancell, making it a good comparator for valuation purposes. Although Inovio also manufactures its own electroporation technology, it only has one proprietary vaccine platform (SynCon) on which there is little clinical data in cancer patients available. This contrasts with Scancell, which has two proprietary immunotherapy platforms. Despite this, Inovio is trading on an EV which 13.1x greater than the EV of Scancell. On page 46, we provide a table showing the comparative data for a group of relevant quoted peer companies. This suggests that there is considerable upside potential for Scancell.

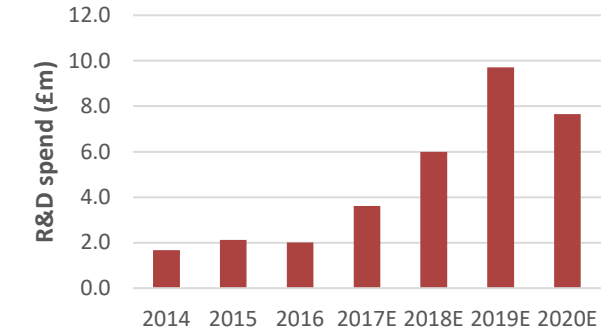
SWOT analysis

Scancell – strengths and weaknesses



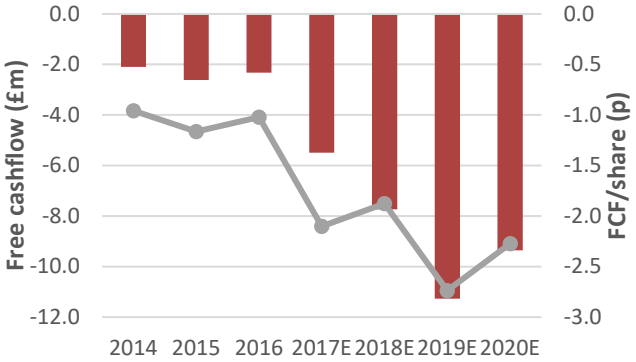
Source: Hardman & Co Life Sciences Research

R&D investment



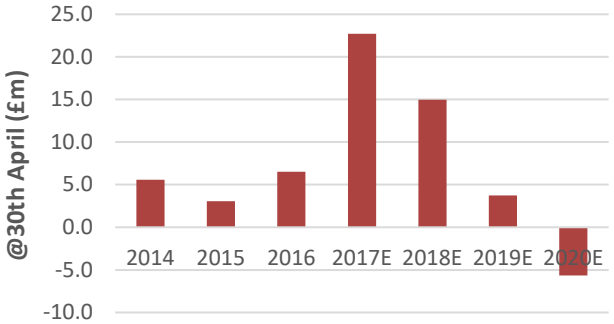
- In recent years, Scancell has invested about £2m per annum in R&D
- From 2009-16, the cumulative R&D investment has been ca.£11m
- Future investment is expected to increase significantly to take both platforms further into clinical development
- A Phase IIb trial for SCIB1 in combination with a checkpoint inhibitor is scheduled to start in 3Q 2017

Free cashflow



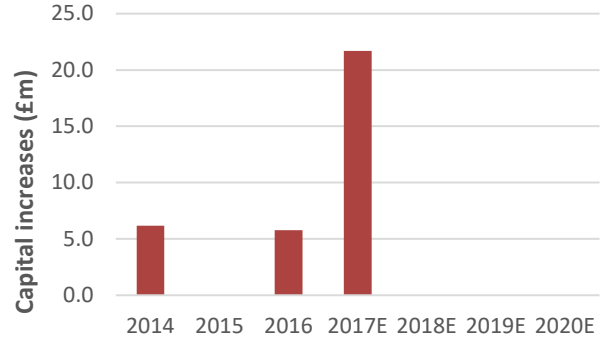
- Given that Scancell is semi-virtual company outsourcing most of its activities, the cash burn is directly related to R&D investment and administration costs
- There will be a modest increase in costs to prepare for the upcoming clinical trial programme
- The company has opened a US office in San Diego and an office in Oxford to coordinate US and EU clinical trials respectively

Net cash/(debt)



- At 30th April 2016, Scancell had net cash of £6.5m
- Given the planned clinical trial programme, we are assuming that the company raises up to $30m/£22m new capital by the end of fiscal 2017

Capital increases



- The company has raised £18.9m through share issues since incorporation to get it where it is today
- The most recent capital increase was £6.2m to fund the preparation needed for the upcoming clinical trial programme for SCIB1, SCIB2 and Modi-1
- Our forecasts assume that Scancell raises ca.$30m/£22m gross new funds by the end of fiscal 2017

Source: Company data; Hardman & Co Life Sciences Research

Background to cancer

Epidemiology

The toll of cancer – US

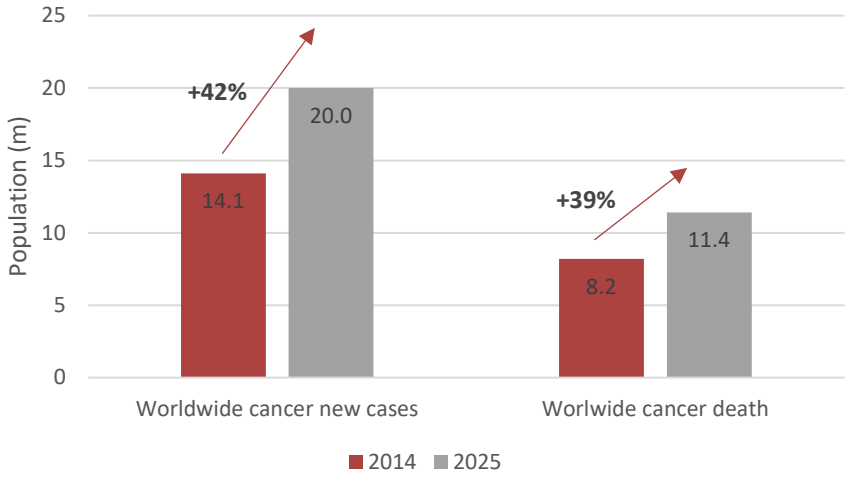
Source: American Cancer Society

Cancer is a worldwide problem. There were an estimated 14.1 million new cases globally in 2012, and this number is forecast to rise to 20 million by 2035[1]. This increase is mainly due to the growing global population and increased life expectancy. The five most common cancers (lung, breast, colo-rectal, prostate and stomach) account for nearly 50% of all cases.

The frequency of cancer increases with age, with relatively few people acquiring cancer before the age of 30 years. This is partly because it can take many years to acquire the multiple abnormalities that generate cancer cells. Furthermore, the probability of being exposed to the risk factors for cancer also increases with time.

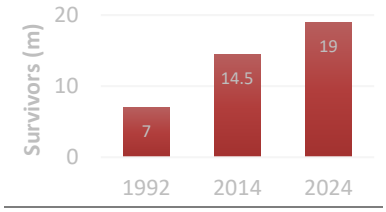
An estimated[2] one-third of the world's population will develop cancer of some kind during their lifetime and about 70% of those who do will die from the disease. From 2014 to 2025, the anticipated rise of 42% in cancer new cases will lead to an increase in cancer deaths of 39%, and most of the burden of the cancer incidence and mortality will be borne by low and middle income countries.

Impact of cancer worldwide



Source: World Cancer Report 2014, www.cancer.gov[2]*, Hardman & Co Life Sciences Research*

Cancer survival



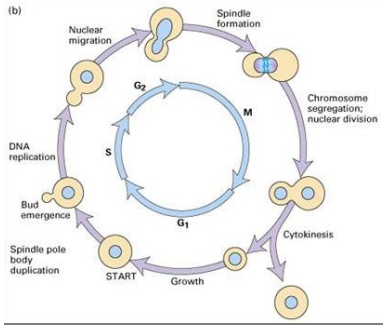
Source: www.cancer.gov

Improving survival rates

Over the last 30 years, considerable progress has been made in the fight against cancer. The overall age-adjusted cancer mortality rates for most cancers has dropped steadily in the US and other developed countries.[2] This is mainly due to the reduction of tobacco consumption, an improvement of cancer diagnosis and the introduction of new drugs. According to the American Cancer Society, the number of cancer survivors in the US, has increased from ca.3.0 million in 1971 to 13.7m in 2012[3] and 14.5m in 2014. Despite the great progress that has, and continues, to be made against cancer. It remains the second leading cause of death in the US, accounting for nearly 1-in-4 deaths.

[1] www.wcrf.org
[2] www.cancer.gov
[3] American Cancer Society

Cell cycle progression



Source: www.pha.jhu.edu

Cancer biology

Cancer is a term that describes a number of diseases in which abnormal cells grow and divide in an unregulated way. The malfunction is caused by damage to a number of regulatory mechanisms and genetic disorders within the cell which ultimately form a tumour, an abnormal mass of tissue which can be:

- **Benign** (non-cancerous) – Does not have the ability to invade and metastasise
- **Cancerous** – Unregulated cancer cells grow and multiply, with the aptitude to invade nearby tissues and spread around the body (metastasis)

Metastasis occurs when cells become detached from the initial tumour and are carried through the bloodstream and lymphatic system to other parts of the body, forming a secondary cancer. This eventually interferes with the normal functioning of cells and organs which can lead to the death of the patient. An estimated 60% of all cancer patients have some sort of metastasis at diagnosis.

Diagnosis

Early diagnosis is key

Early diagnosis is a key factor for obtaining a positive prognosis – the earlier that the cancer is diagnosed, the better chance of a successful outcome. It is essential to identify the problem before it has had the chance to metastasise and spread to other parts of the body. Great strides have been made in recent years with the advent of molecular diagnostics, which allow genotyping to identify 'at risk' patients and early diagnosis using DNA-based tests can detect the presence of cancer from a very small number of cells.

Treatment

Treatment of cancer relies on three core approaches:

- **Surgery** – Ablation of the tumour
- **Radiation** – X-ray, proton therapy
- **Chemotherapy** – Use of cytotoxic drugs

Depending on the type of cancer, treatment is often in the form of a multidisciplinary approach. This is increasingly the case as new options have emerged, making the chemotherapeutic approach much more refined than simply blasting cells with very toxic drugs in an unspecific manner.

Targeted approaches

Approach	Comment
Hormonotherapy	For hormone sensitive or hormone dependent cancers
Immunotherapy	Use own immune system to fight the disease
Precision medicine	Tailored patient treatment based on genotyping
Stem cell transplant	Allows higher doses of chemotherapy

Source: Hardman & Co Life Sciences Research

Biological therapies

There are currently 23 regulatory approved antibody drugs for cancer

There is little doubt that the greatest advance over the last decade has been the use of biologics, changing the whole approach to cancer therapy. Of the 53 regulatory approved drugs derived from monoclonal antibodies, 23 are for cancer. With ImmunoBody and Moditope, Scancell is seeking to harness the mechanisms of the body's own immune system to target cancer and its pathways. As precision and personalised medicine comes increasingly to the forefront, drug companies are homing in on tumours using highly targeted therapeutic approaches.

Immuno-oncology

Immuno-oncology uses the body's own immune system to fight cancer

The immune system is programmed to recognise self from non-self. It has mechanisms in place to down-regulate itself in order to prevent normal, healthy cells from being harmed and to up-regulate if a foreign element is identified. Immuno-oncology (IO) is the use of the patient's own immune system to fight cancer.

Over the last 30 years, better understanding of both immunology and oncology has brought immense hope in the fight against cancer and it has now become the fastest moving component in cancer therapy. No week passes without a new success story, a breakthrough or a new clinical trial being launched somewhere in the world. Immuno-oncology is based on the principle of stimulating the patient's own immune system to recognise 'non-self' cells and to generate or increase an anti-tumour immune response in order to control or eradicate them.

If this is the case, the question arises as to why the immune system does not try to eliminate cancer cells on its own? There are thought to be a variety of cellular and environmental reasons why the immune system appears to be ineffective in eliminating or suppressing cancer, including:

- The immune system may have difficulty discerning the difference between normal cells and cancer cells
- The immune system is not strong enough to give a response and eradicate the cancer cells
- The antigen-specific cytotoxic and helper T-cells may be ineffective if cancer cells evade detection through producing proteins that suppress the initial immune response
- Other inhibitory processes (metabolic, cytokines, suppressor cells) are present

Three main approaches

Very dynamic area of drug development…

The term 'immuno-oncology' encompasses several different treatment approaches, each of which has a distinct mechanism of action. However, all of them are designed to boost or restore immune function in some way[4]. Whilst it is a relatively new approach, immuno-oncology represents a dynamic area providing a number of possibilities and targets of which the following three are the main focus of activity:

…with 2,500 active clinical trials…

- Monoclonal antibodies – including checkpoint inhibitors
- Therapeutic cancer vaccines/T-cell stimulators
- Chimeric antigen receptor T-cells (CAR-T-cells)

…of which over 350 are for cancer vaccines

Putative drug therapies based on immunotherapy are filling the R&D pipelines of many pharmaceutical and biotechnology companies. According to the *clinical trials.gov* website and Cortellis Clinical Trials Intelligence[5], there are currently ~2,500 active clinical trials in the field of immuno-oncology, with one-third involved in the testing next generation therapeutic cancer vaccines (T-cell activation) and checkpoint inhibitors. There are currently c.350 ongoing clinical trials for therapeutic cancer vaccines.

[4] Mellman et al., Nature, 2011
[5] Cortellis Clinical Trials Intelligence 2016

Using an active approach (i.e. produced in the body) rather than passive production (e.g. external modification and/or production of proteins, cytokines, T-cells, or monoclonal antibodies that are then administered into the body), the products work in a way more akin to the natural immune response and function within the boundaries and controls of the immune system.

Scancell has two distinct and flexible technology platforms, both involved in the field of therapeutic cancer vaccines to produce high avidity T-cell activation and anti-tumour responses.

Therapeutic cancer vaccines

The aim is to obtain high avidity T-cell responses

Therapeutic cancer vaccines, or T-cell activators, are cancer cells, parts of a cancer cell or chemically pure antigens that prompt increased immune response in the patient's body. They stimulate the immune system to produce cytotoxic T-cells that attack cancer cells that have those antigens with the expectation that this will lead to improved survival. Historically, the development of therapeutics anti-cancer vaccines has been hampered by high failure rates that can be attributed, in part, to their failure to generate a high avidity anti-tumour T-cell response.

It is important to note that the primary goal of a therapeutic vaccine is to generate an active immune response against an existing cancer, whereas a preventative vaccine is targeted at infectious diseases and aims to prevent disease in the first place. Successful commercially available preventative vaccines include Gardasil and Recombivax (both from Merck & Co) and Cervarix and Engerix-B (both from GlaxoSmithKline).

There are only two therapeutic cancer vaccines on the market

To date there have been only two cancer therapeutic vaccines approved by the regulators Provenge (Dendreon) and Imlygic (Amgen). Provenge is designed to boost the immune system to attack prostate cancer cells. It uses and autologous approach and is, therefore, customised for each patient (white blood cells are collected from the blood and sent to a lab, where they are exposed to a protein from prostate cancer cells called prostatic acid phosphatase (PAP). The engineered cells are then reinfused back into the patient. This process is undertaken three times by each patient). It is time consuming and expensive.

In contrast, Imlygic is a genetically modified oncolytic viral therapy which, if the tumour cells have not been removed surgically, is injected directly into the lesions of patients with recurrent melanoma. Some reports suggest that the virus induces chronic abscesses which are both painful and also risk causing further metastases.

Regulatory approved cancer vaccines

Preventative	Therapeutic
Cervarix – cervical cancer	Imlygic – melanoma
Engerix-B – hepatitis B	Provenge – prostate cancer
Gardisil – cervical cancer	
Recombivax – hepatitis B	

Source: Hardman & Co Life Sciences Research

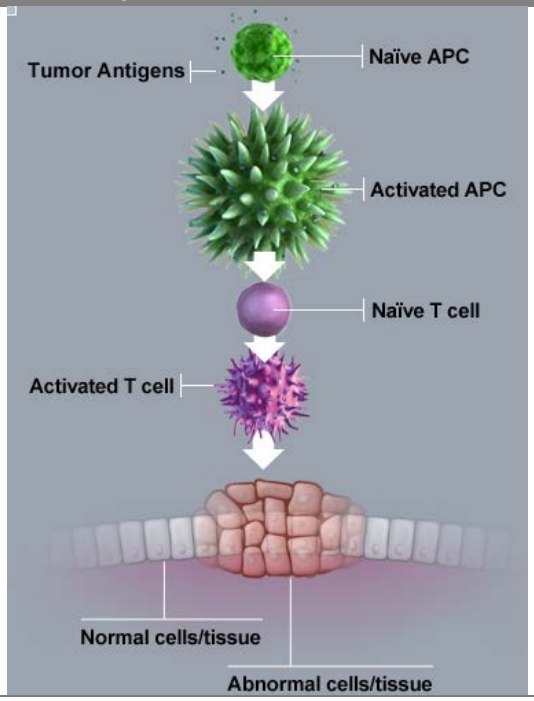
The aim is to generate the antigen in-vivo…

…which is then processed by the APC

Generally speaking, the beauty of plasmid DNA immunotherapy is its indirect approach to immune activation. Instead of injecting directly into the tumour, the plasmid is injected into a limb muscle where it produces the antigen *in vivo* which is processed by the APCs to initiate a T-cell driven immune response[6].

[6] Abbas & Lichtman, 2011

Stimulation of immune system



APC = antigen-presenting cell
Source: Abbas and Lichtman

The immune system vs cancer cells

Cancer cells can carry tumour associated antigens, oncofetal antigens, and antigens that are referred to as neo-antigens, which mark cancer cells as 'abnormal' or foreign in order to trigger the immune response by killer T-cells.

- **Tumour associated antigens** are made in much larger quantities by cancer cells than normal cells, or are antigens that are not normally made by the tissue in which the cancer developed (for example, antigens that are normally made only by embryonic tissue but are expressed in an adult cancer). They alert the immune system to the dysregulated tissues
- **Newly formed antigens** (neo-antigens) – result from gene mutations in cancer cells and then are viewed as foreign by the immune system
- **Modified neo-antigens** – result from enzymes which are triggered by cellular stress to alter amino acids which rapidly alert the immune response

However, several factors may make it difficult for the immune system to target growing cancers for destruction:

- Many cancer-associated antigens are only slightly altered versions of self-antigens and therefore may be hard for the immune system to recognise.
- Cancer cells may undergo genetic changes that may lead to the loss of cancer-associated antigens and then evade the immune response.
- Cancer cells can also evade anti-cancer immune responses by providing an immuno-suppressive environment by secreting immuno-suppressive messengers like cytokines

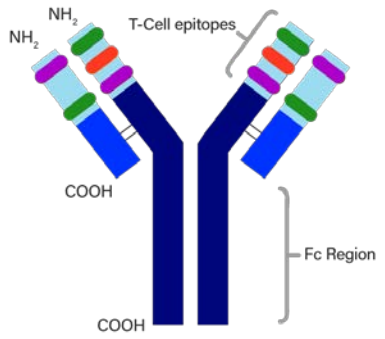
Overall, the development of cancer vaccines is a new field in the weaponry against cancer, which is where Scancell's activities are focused.

Scancell technologies

Scancell is developing two flexible immuno-oncology platforms, each adopting a different approach for the treatment of cancer. They do not compete with each other and will actually bring different options in targeting various types of tumours.

ImmunoBody®

ImmunoBody antibody

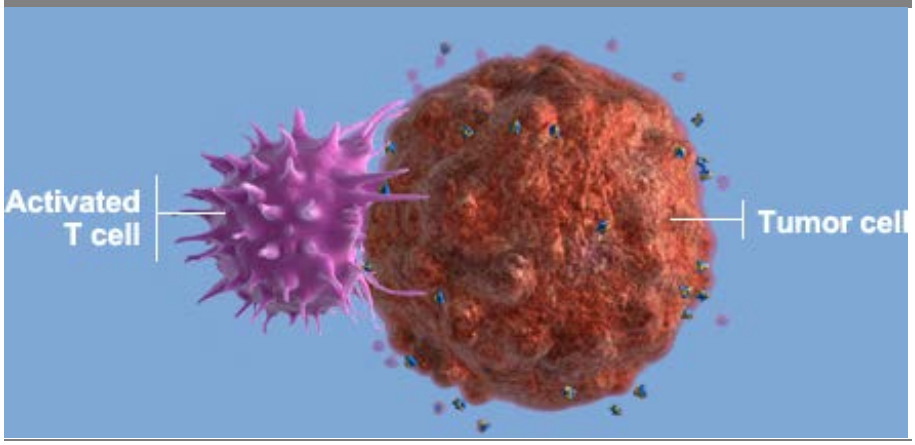


Source: Scancell

Scancell's ImmunoBody technology generates high avidity tumour killing T-cell responses that target and eliminate tumours with a magnitude superior to that generated by currently approved vaccines. Each ImmunoBody therapeutic vaccine can be designed and customised to target a particular cancer in a highly specific manner. It also offers the potential for enhanced avidity of the T-cell response resulting in better efficacy and safety compared with more conventional approaches.

An ImmunoBody is a DNA plasmid that encodes a human antibody engineered to express epitopes from tumour antigens over-expressed by cancer cells. Antibodies are ideal vectors for carrying T-cell epitopes to tumour antigens as they have a long half-life and can target dendritic cells via their Fc receptors, allowing efficient stimulation of both helper and cytotoxic T lymphocyte (CTL) responses. The helper T-cells overcome the immunosuppressive tumour environment and greatly increase the population of killer T-cells which attack the tumour site. The potency of T-cells is measured by avidity or the ability to recognise low amounts of antigen processed and presented on MHC. As tumour cells express very low levels of any one peptide MHC combination, it is necessary to generate high avidity T-cells to allow recognition and tumour lysis.

Activated T-cells – Mode of action

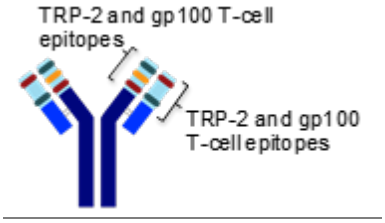


Source: www.fightcancerwithimmunotherapy.com

Features

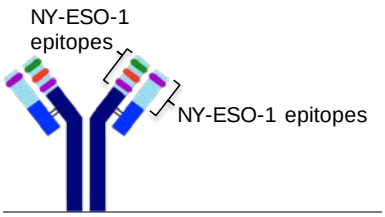
- Multiple tumour 'target antigens' (T-cell epitopes) that are engineered into a single antibody framework
- Customisation and targeting different tumour types can be achieved by grafting different T-cell epitopes into the framework
- The vehicle is efficiently taken up by cells involved in triggering T-cell responses (antigen presenting cells) by the antibody tail (Fc region)
- ImmunoBody can be delivered as a DNA plasmid that is flexible, easy to manufacture and inexpensive

SCIB1



Source: Scancell

SCIB2



Source: Scancell

The ImmunoBody structure is able to enclose 12 different T-cell epitopes. If CD4 and CD8 epitopes are nested, then this could be increased further. Therefore, ImmunoBody could target multiple antigens and all common human leukocyte antigen (HLA) types.

The major advantage of the ImmunoBody technology is that the Fc (constant region) component of the engineered antibody will be recognised by the high affinity CD64 receptor present on activated APCs. The antibody is then internalised and processed by the APC, resulting in a significant enhancement of both the frequency and avidity of the T-cell immune response. Previous studies have shown that Fc receptor internalisation of antigen-antibody complexes is 1,000 fold more efficient than pinocytosis for stimulation of helper T-cell responses.

Scancell is developing two products using its ImmunoBody platform – SCIB1 and SCIB2. This platform has the flexibility to swap epitopes targeting one type of cancer for epitopes targeting another type of cancer thereby creating a different DNA vaccine.

SCIB1 and SCIB2 ImmunoBodies

ImmunoBody	SCIB1	SCIB2
Indication	Malignant melanoma	Non-small cell lung cancer
Stage	Phase I/II	Pre-clinical
Description	SCIB1 ImmunoBody encodes two CD8 epitopes from the melanoma antigens TRP-2 and gp100 plus two CD4 epitopes from gp100	SCIB2 ImmunoBody encodes sixteen NY-ESO-1 T-cell epitopes

Source: Hardman & Co Life Sciences Research

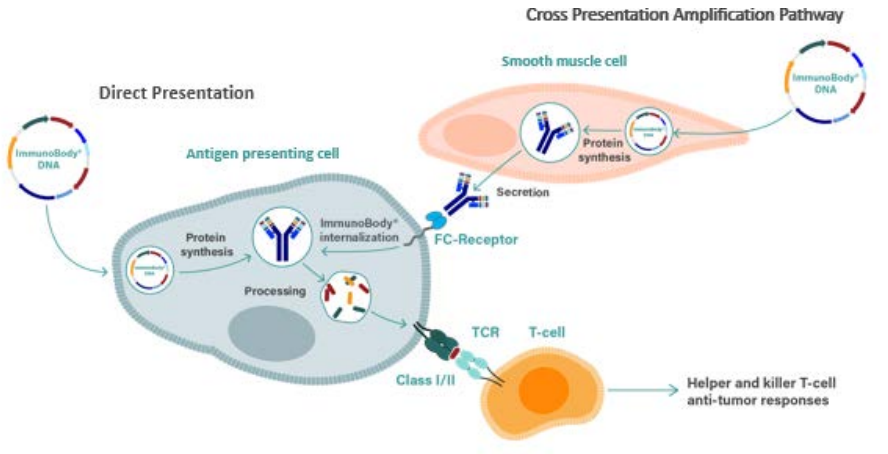
Dual mechanism of action of ImmunoBody

Dual mechanism of action

Two presentation mechanisms work synergistically to produce 100x greater T-cell responses

The combination of direct and cross presentation by ImmunoBody results in amplification of the immune response, inducing high frequency, high avidity T-cells that deliver a potent anti-tumour effect via the high CD4 and CD8 avidity. The synergistic effect of this dual mechanism is to produces 100x greater T-cell responses.

ImmunoBody – Dual mechanism of action



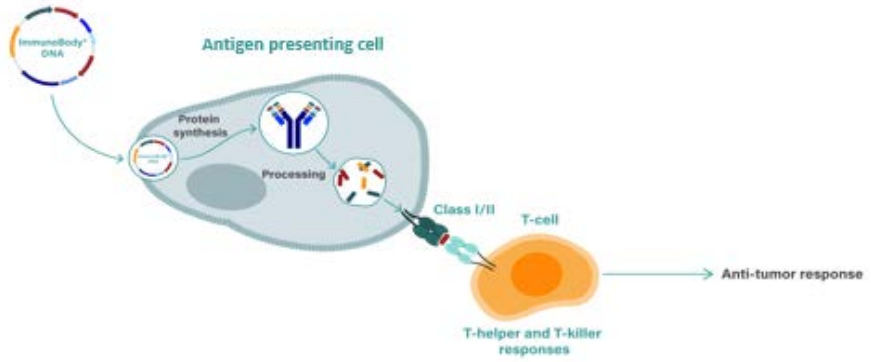
Source: Scancell

Direct presentation only produces moderate avidity T-cell response…

Direct presentation

The ImmunoBody DNA targets antigen-presenting cells (APCs) directly via transfection. The DNA is transcribed, translated and then the antibody is processed. The tumour-specific T-cell epitopes are presented via the major histocompatibility complex (MHC) Class I and II molecules to $CD4^+$ and $CD8^+$ T-cells. The immune response generates only moderate T-cell avidity which is too weak to produce an anti-tumour effect in an immunosuppressed environment.

ImmunoBody – Direct presentation



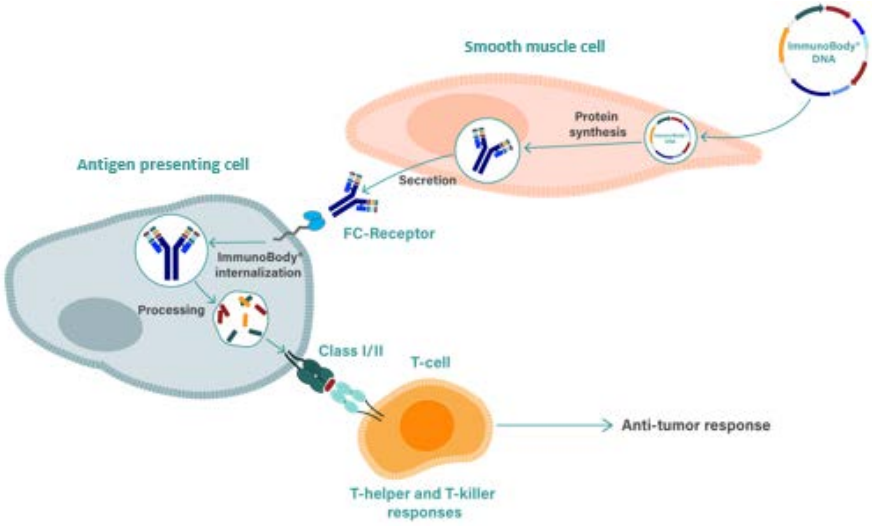
Source: Scancell

…and so does cross presentation…

Cross presentation amplification pathway

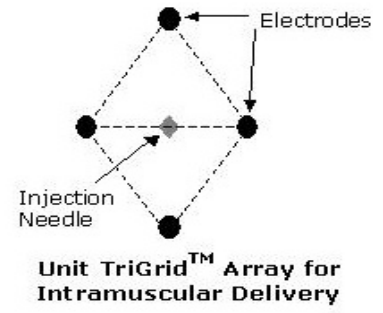
The ImmunoBody DNA also transfects other (non-APC) cells, which then secrete the antibody protein which targets APCs' CD64 receptors via the high affinity Fc component. The antibody is internalised, cleaved and the epitopes are presented via the MHC Class I and II molecules to the $CD4^+$ and $CD8^+$ T-cells. As in the previous mechanism, the immune response gives a low T-cell avidity which is too weak to trigger an effective anti-tumour response.

ImmunoBody – Cross presentation



Source: Scancell

Electroporation delivery



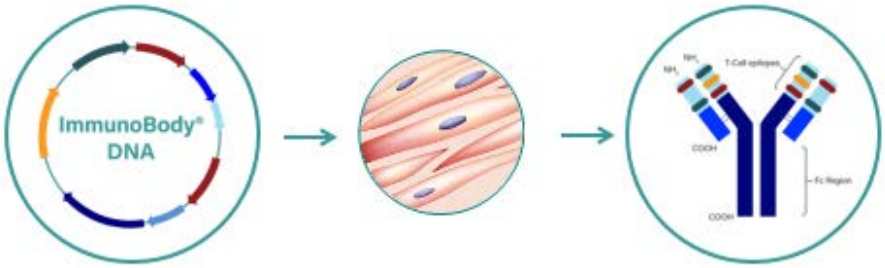
Source: Ichor Medical Systems

Electroporation

Most drugs act once they have been absorbed into a cell. However, cells are designed to resist the entry of anything foreign in order to protect themselves. Therefore, the delivery of DNA or nucleic acids directly into a cell through the cell's protective membrane has been a significant challenge.

Scancell's immunotherapies are delivered into muscle cells of the body in a small local area of tissue using electroporation (EP) delivery technology. EP uses brief, locally applied, controlled electric pulses to create temporary and reversible permeability, or pores, in the cell membrane. Scancell uses the patented TriGrid electroporation delivery system from Ichor Medical Systems to creating an electric field in a reproducible manner.

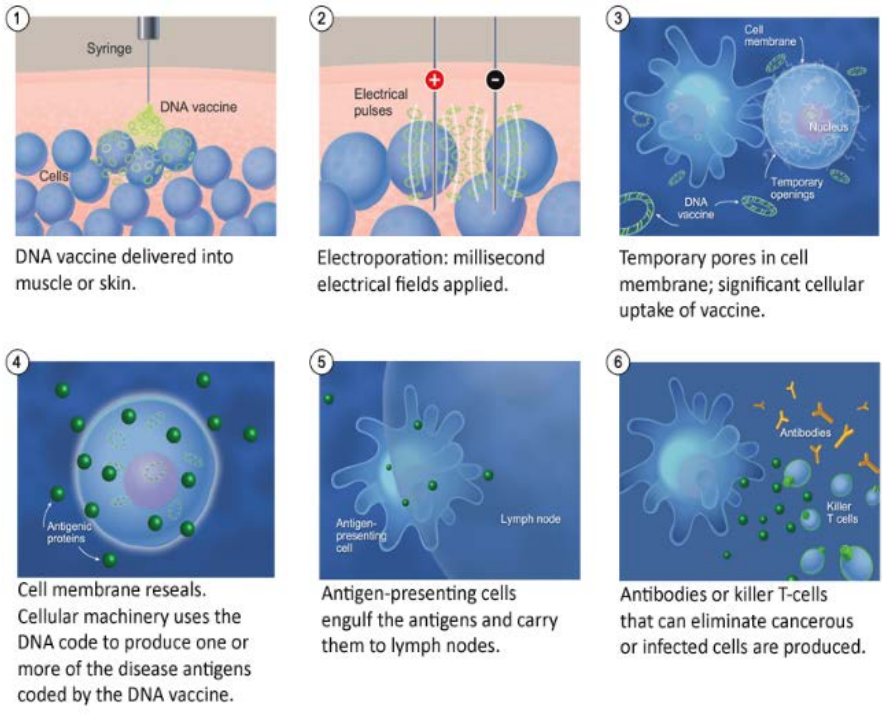
Delivery of ImmunoBody platform



Source: Scancell

The electroporation delivery technique is well demonstrated in the following graphic for delivery of SynCon® (Inovio). EP increases the cellular uptake of the DNA plasmids by at least 1,000-fold compared to the delivery of "naked DNA" alone.

Electroporation delivery



Source: Inovio Pharmaceuticals Inc

SCIB1 in malignant melanoma

The SCIB1 proof-of-concept trial started in 2010…

…aiming to recruit 35 patients in two parts

Scancell's lead candidate using the ImmunoBody platform is SCIB1, which induces T-cells with sufficient avidity to cause tumour regression in patients with melanoma. SCIB1 is a DNA plasmid encoding 1 TRP-2 epitope and 3 gp100 T-cell epitopes within a human IgG1 antibody. In a phase I/IIa trial, SCIB1 was injected into muscle using the electroporation method of administration.

SCIB1 Phase I/II clinical trial

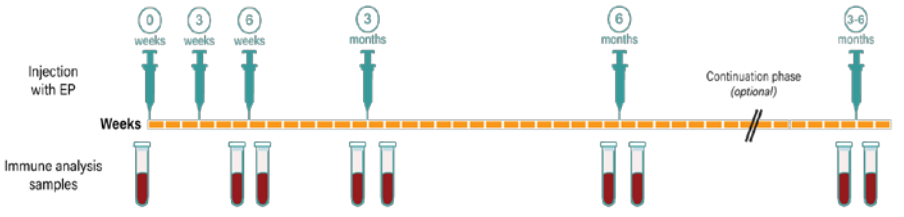
A phase I/II trial (SCIB-001) enrolling 35 patients was designed to evaluate the safety, maximum tolerated dose, and immunogenicity of SCIB1 in patients with resected or inoperable melanoma. This study was divided into two parts:

- **Part 1:** Dose escalation in 16 patients with stage III/IV melanoma
  - – Primary objective: safety and tolerability
  - – Secondary objectives: immune response and tumour response
  - – Safety assessment performed after three doses (0.4mg, 2mg, 4mg and 8mg)
- **Part 2:** Extension phase in 19 patients with 18 having fully resected stage III/IV melanoma
  - – Primary objective: safety and tolerability
  - – Secondary objectives: immune responses and disease free survival
  - – 14 patients received 4mg; 5 received 8mg

The study schedule is described as follows:

- Patients dosed at Weeks 0, 3 and 6 weeks with boosts at 3 and 6 months
- Immune samples taken pre- and post-dosing
- Optional continuation phase with dosing every 3-6 months for up to 5 years

SCIB1 – Phase I/IIa study schedule



Source: Scancell

Trial outcome to date

Safe + well-tolerated…

…and 15/16 patients alive after median 49 months…

…unprecedented outcomes!

Overall, the immune responses induced were more consistent in patients with fully-resected disease, suggesting that SCIB1 may confer protection from recurrence of melanoma in resected patients with little associated toxicity. The safety and tolerability of SCIB1 was well recognised by the regulatory body as evidenced by an agreed extension of treatment for up to five years. To date, SCIB1 has produced a 49 months' median observation time associated in 15/16 (94%) fully resected patients, which is an unprecedented outcome and "well beyond established norms"[7].

[7] Dr Keith Flaherty, Massachusetts General Hospital

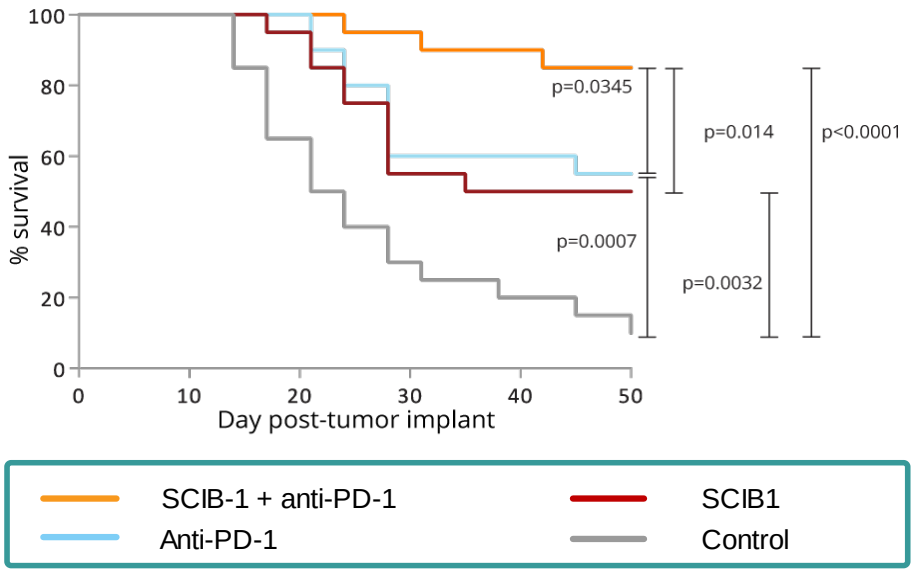
- No maximum tolerated dose was determined as the highest dose received was well tolerated with no serious adverse effects
- Immunisation with SCIB1 by electroporation induced T-cell responses in 24/28 (86%) patients
- Clear dose response
- With more than 220 injections administered to patients, SCIB1 shows better tolerability compared to standard-of-care (patients experienced 13% and 20% grade 3-5 adverse events with pembrolizumab and ipilimumab, respectively)
- No serious adverse events leading to discontinuation of the treatment and no dose-limiting toxicities
- More potent responses were seen in fully-resected patients than in patients with macroscopic disease
- 15/16 fully-resected patients (2-4mg dose) showed a high avidity T-cell response and are still alive with a current minimum observation time of three years, and a median observation time of 49 months. Only four of the surviving patients have received additional treatment following SCIB1 immunisation

Combination of SCIB1 with a PD-1 checkpoint inhibitor

Scancell expects SCIB1 to improve the clinical outcomes of checkpoint inhibitors

Although the SCIB1 trial showed that patients with low tumour burden responded well to this therapy, patients with more advanced disease may benefit from using this drug in combination with a checkpoint inhibitor. Checkpoint blockade has demonstrated anti-tumour responses in approximately 20-40% of melanoma patients. However, the majority of patients are non-responders and do not stimulate a sufficiently large immune response. These patients may benefit from an effective vaccine that stimulates high avidity T-cell responses prior to checkpoint blockade.

Comparison of SCIB1 alone or with PD-1 antibody



Source: Scancell

This is not a new concept. Bristol-Myers Squibb is running a Phase III trial with MDX-1379 (2 gp100 peptides vaccination) in combination with ipilimumab (CTLA-4 inhibitor) and showed that this peptide vaccination did not generate T-cells with sufficient avidity to eradicate the tumours.

In an *in vivo* study (see graphic above), vaccination of HLA-DR4 transgenic mice with SCIB1, high frequency and avidity T-cell responses were induced which resulted in survival (45%) of mice with poorly immunogenic B16F1-DR4 tumours. Scancell demonstrated that SCIB1 vaccination was associated not only with increased infiltration of CD4 and CD8 T-cells within the tumour but also associated with upregulation of PD-L1 within the tumour environment. PD-1 blockade also resulted in increased CD8 T-cell infiltration and an anti-tumour response with 50% of mice showing long term survival. In line with the hypothesis that PD-1/PD-L1 signalling results in inhibition of proliferation of high avidity T-cells at the tumour site, the combination of PD-1 blockade with SCIB1 vaccination enhanced the number and proliferation of the CD8 tumour infiltrate. This resulted in a potent anti-tumour response with 85% survival of the mice.

Design of Phase IIb combination trial

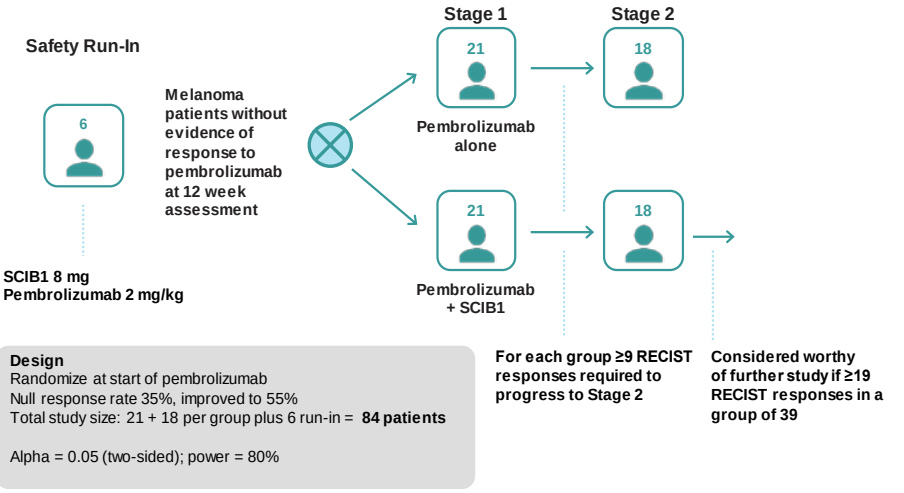
Phase IIb combination study to start in 3Q 2017 in advanced melanoma…

A phase IIb clinical trial enrolling 84 patients has been planned and is expected to start in 3Q 2017 in order to provide further proof-of-concept for the whole ImmunoBody platform. The study will assess the effect of SCIB1 in combination with a checkpoint inhibitor in patients with melanoma. The expectation is that such a combination will increase the response rate to at least 50%.

Part 2 will be a fully randomised trial

Initially, the safety and tolerability of SCIB1 in combination with the anti-PD-1 antibody will be assessed in a small cohort of patients (n=6) and followed up at 12 weeks. On the back of a positive outcome, efficacy and safety of the combination with be compared to that for the checkpoint inhibitor alone in a randomised fashion. The primary end-point will be immune-related response rate; with secondary end-points including overall response rate, duration of response and progression-free survival at 6 months. This trial will be led by Dr Flaherty (Harvard Medical School).

SCIB1 + PD-1 phase IIb trial protocol



Source: Scancell

Advantages of SCIB1 over established treatments

The number of worldwide open study clinical trials on melanoma as at May 2016 was 523[8], which highlights just how crowded this field of development is, whilst also confirming that there is an unmet medical need. Amongst these trials, 43 involve the testing of DNA therapeutic vaccines.

[8] www.clinicaltrial.gov

Compared to previous clinical trials with peptide vaccines, SCIB1 clearly has an advantage regarding recurrence-free survival and the overall survival rate. Moreover, the five year treatment continuation granted by the regulators for the proof-of-concept clinical trial demonstrates its confidence in the safety and tolerability of SCIB1.

SCIB1 asset is likely to be out-licensed

Despite these excellent results compared to established melanoma drugs, given the size and resources of Scancell, coupled to the competitive area of new melanoma treatments, it is unlikely that the company will develop SCIB1 (or its follow-up SCIB1 PLUS) further for this indication on its own. When all the clinical data is to hand, Scancell will look to out-license this asset in order to maximise value for shareholders.

Recurrence-free survival (RFS) and overall survival (OS) at 3 years

Fully resected	SCIB1		Peptide vaccine		Yervoy		Untreated/placebo	
melanoma patients	RFS	OS	RFS	OS	RFS	OS	RFS	OS
Stage III/IV[9]	69%	94%	52%	79%				
Stage III[10]	67%	100%			47%	TBD	35%	TBD
Stage IV[11]	71%	86%					16%	36%

RFS: recurrence-free survival; OS: overall survival; TBD: to be determined
Source: Scancell, [9]Slingluff et al 2011; [10]Eggermont et al 2015; [11]Sosman et al 2011

SCIB1 summary

Event	Comment
Long term clinical data	► SCIB1 has been given to patients continuously for up to 38 months with regulatory approval to treat for up to 5.5 years ► 70% recurrence free survival at 4 years in resected Stage III/IV patients receiving 2-4mg doses ► Only one patient with Stage III/IV resected disease has died since the trial started ► Median observation time of 49 months in 2-4mg dose patients with resected disease
Safety profile	► Well tolerated with no serious drug related adverse events over up to 38 months' administration ► SCIB1 has been administered on over 220 occasions ► SCIB1 safety is expected to be suitable for combination with checkpoint inhibitors ► No withdrawal due to side effect (cf Yervoy has had 50% withdrawals and 5 drug related deaths)
Ease of manufacture	► Significant cost benefit versus cell therapy vaccines and straight-forward manufacturing process
Business model/ Reimbursement positioning	► Direct injection into patient for in-office administration. Suitable for use by both dermatologists and oncologists ► No complex cell therapy manufacture
Limited cost and time value elevating event	► Widely conceded that checkpoint inhibitors require combination therapy ► SCIB1 DNA vaccine mechanism and safety profile ideal for checkpoint combination

Source: Hardman & Co Life Sciences Research

[9] Slingluff et al 2011
[10] Eggermont et al 2015
[11] Sosman et al 2011

SCIB1 manufacture

For the Phase I/II clinical trial, SCIB1 was manufactured by Cobra Biologics in one of its GMP approved facilities based in Keele, UK. Cobra is an internationally recognised contract manufacturing organisation that provides GMP grade biologics and pharmaceuticals for pre-clinical, clinical and commercial supply.

SCIB1 drug product supply

Trial material was stable for seven years

In June 2016, Scancell announced the suspension of SCIB1 dosing as the stored batch was no longer within the original specification. Eight patients in the long term extension arm of the Phase I/II trial SCIB-001 are affected, but management is anticipating that the anti-tumour response should persist.

Although this did represent a setback, it is worth mentioning that the original batch used in the SCIB1-001 trial was manufactured and has been in storage until required in the trial for up to seven years, indicating the high stability of this DNA-based immunotherapy. Moreover, some of the patients have been receiving SCIB1 vaccine for over four years, showing that it is extremely well tolerated.

Specialist GMP manufacturer appointed with new material expected in 6-9 months

Scancell responded to this news quickly, and in July 2016 it signed an agreement with a specialist DNA contract manufacturer – Eurogentec SA. This experienced and fully accredited GMP manufacturer adds considerable credibility. Management is expecting to receive a new batch of SCIB1 in approximately six months' time. This suggests that the planned Phase II trial in combination with a checkpoint inhibitor will commence in 3Q 2017.

SCIB1 –Orphan Drug status

The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.

In February 2014, the FDA granted SCIB1 Orphan Drug designation for the treatment of metastatic melanoma. The terms allow Scancell a 50% tax credit for clinical trials, a waiver of the prescription drug user fee when the filing is made and a period of seven years of market exclusivity following drug approval. During this period, the FDA will not approve a New Drug Application (NDA) or a generic drug application for the same product.

SCIB1 PLUS

Scancell is currently investigating SCIB1 PLUS, an improved version of SCIB1. This newer version is based on a revised ImmunoBody with further epitopes, to allow treatment of the majority of patients, rather than only those with the HLA-A2 immune sub-type. The use of SCIB1 PLUS would avoid the need for HLA testing and also double the size of the potential market. It may be particularly relevant for the treatment of the very large number of patients with resected melanoma ie the adjuvant indication. In order to pursue SCIB1 PLUS in clinical trials, a small safety study may be needed prior to efficacy studies.

SCIB2 immunotherapy

SCIB2 trial will be in NSCLC

In parallel with the development of SCIB1, Scancell is developing a second therapeutic vaccine SCIB2, also based on the ImmunoBody platform, for use in non-small cell lung cancer (NSCLC).

SCIB2 rationale

SCIB2 uses the ImmunoBody platform to target tumours expressing the NY-ESO-1 antigen. NY-ESO-1 has restricted expression in normal cells and is over-expressed in tumour cells – non-small cell lung cancer patients 18%; prostate 39%; and bladder cancer 35%. There is also over-expression of NY-ESO-1 in oesophageal, liver, melanoma, ovarian and breast cancer. A variety of vaccination approaches targeting NY-ESO-1 have been tried using synthetic peptides, recombinant proteins and DNA encoding full length NY-ESO-1, but they have all failed to control tumour growth and induce high T-cell avidity.

Pre-clinical results

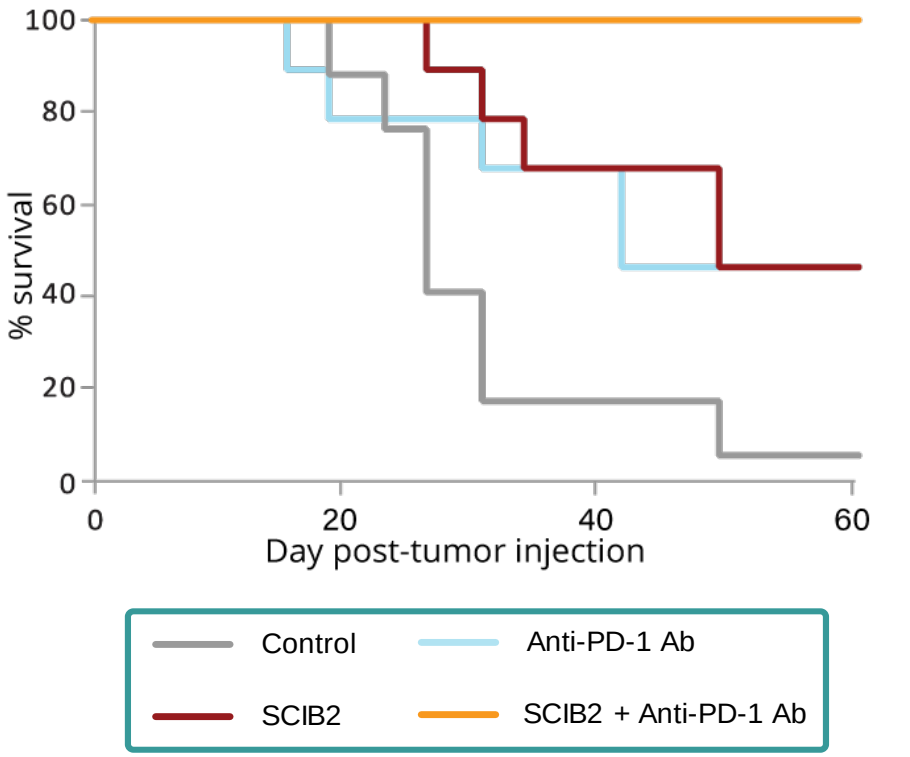
SCIB2 could be used alone or in combination…

Pre-clinical data is available to support the clinical development of SCIB2 either alone or in combination with a checkpoint inhibitor.

…based on pre-clinical data

SCIB2 is a DNA plasmid encoding sixteen NY-ESO-1 T-cell epitopes, covering over 80% of Human Leukocyte Antigen (HLA) phenotypes, within a human IgG1 antibody that aims to stimulate high avidity T-cell responses. In an *in vivo* study using HHDII transgenic mice, SCIB2 generated high frequency CD8 and CD4 responses, similar to SCIB1.

Use of SCIB2 alone or with PD-1 antibody



Source: Scancell

- Immunisation with SCIB2 generates strong NY-ESO-1 specific CD8 and CD4 responses in HLA transgenic mice
- SCIB2 induces higher avidity CD8 responses than peptide vaccination
- Immunisation with SCIB2 generates strong anti-tumour immunity
- Long term survival was obtained by combining SCIB2 with checkpoint blockade (anti-PD-1 antibodies)
- 100% tumour survival was achieved when combining SCIB2 with PD-1 blockade in the B16/HHDII/NY-ESO-1 tumour model

The 100% tumour survival with the combination of SCIB2 and PD-1 blockade is especially promising as PD-1 blockade is known to have lower associated toxicity when compared to CTLA-4 and PD-L1 blockades.

SCIB2 development plan

Proof-of-concept trial expected to start recruiting in 2018

A phase I/IIa clinical trial using SCIB2 in combination with a checkpoint inhibitor, enrolling 74 non-small cell lung cancer patients, has been planned and is expected to start recruiting during 2018. The patients will be selected for their failure in responding in checkpoint inhibitors. The trial will be divided in two parts:

- Dose escalation and safety assessment of SCIB2 ± checkpoint inhibitor in 18 patients
- Randomised, controlled comparison of SCIB2 + checkpoint inhibitor versus CP inhibitor alone in 56 patients
- Primary outcome measure: Improvement in overall response rate from 15% to 35%

ImmunoBody for glioblastoma multiforme

Scancell announced recently the initiation of a new pre-clinical study using the ImmunoBody platform for the treatment of glioblastoma multiforme (GBM). The investigation is in collaboration with Nottingham Trent University and the University of Portsmouth and the £95,000 study is being funded by the Headcase Cancer Trust, the only UK charity which dedicates its funding solely to research which aims to find a cure for GBM brain tumours.

GBM is a fast-growing glioma that develops from star-shaped glial cells (astrocytes and oligodendrocytes) that support the health of nerve cells within the brain. These are the most invasive type of glial tumours, rapidly growing, and commonly spreading into nearby brain tissue. The median survival is 15 months and only 3 to 5% of people survive after 5 years. GBM has an incidence of two to three per 100,000 adults per annum. In the US, approximately 18,000 people are diagnosed with GBM each year, leading to 13,000 deaths annually. Overall, GBM accounts for about 17% of all tumours of the brain. Treatments are limited and involve surgery, chemotherapy and radiation.

Due to the highly aggressive nature of GBM and the lack of successful curative treatments to date, there is an urgent need for novel therapeutic approaches such as immunotherapy. The vaccine treatment will be assessed for its ability to generate strong anti-GBM tumour immunity, as well as the ability to reduce and eradicate established tumours.

Moditope®

Approach taken with Moditope is entirely different

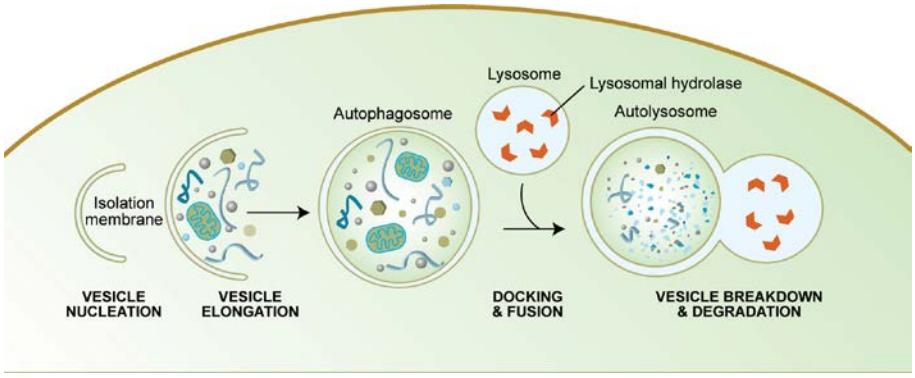
Moditope represents a completely new class of potent and selective immunotherapy agent which could have a profound effect on the way that cancer immunotherapies are developed. It targets the modified self-antigens induced by cellular stress. Essentially, this flexible technology will allow Scancell, either alone or in partnership, to develop more universal cancer treatments. Interest in this novel vaccine approach has gained traction following the acquisition of Padlock Therapeutic by Bristol-Myers Squibb in March 2016 for up to $600m, representing up to a 30x return for shareholders in two years. Padlock was focused on the use of small molecule inhibitors of citrullination for rheumatoid arthritis, whereas Scancell is applying the inverse approach of enhancing the immune response to citrullinated antigens for cancer immunotherapy.

Cancer and citrullination

Autophagy is the orderly way that cell components are degraded and recycled…

Cancer cells are rapidly dividing and require a constant supply of nutrients in order to survive and proliferate. One of the tools used by cancer cells to promote their survival is the natural autophagy mechanism by which cellular components are degraded in an orderly manner and then recycled. This process is essential for growth regulation and the maintenance of homeostasis.

Autophagy – schematic diagram



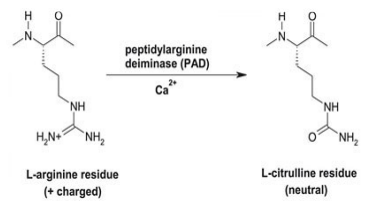
Source: www.wormbook.org

…and is upregulated during cancer progression…

Autophagy is upregulated during cancer progression in response to multiple stresses, including:

- Hypoxia
- Nutrient deprivation
- Extracellular matrix (ECM) detachment
- Endoplasmic reticulum (ER) stress

PAD-mediated citrullination



Source: Hardman & Co Life Sciences Research

With this process, cancer cells digest and modify some of their own proteins through an important set of enzymes: the peptidyl arginine deiminases (PADs). The calcium-dependent hydrolase converts an arginine to its corresponding citrulline, a process known as citrullination, which is the conversion of the positively charged aldimine group (=NH) of arginine to the neutrally charged ketone (=O) of citrulline. The direct effect of citrullination is deactivation of protein by the modification of the 3D shape and charge of the original protein.

...but tumours are able to suppress the immune system

The immune system detects these modified proteins and triggers the CD4+ T-cells response around the body to search out and destroy the cancerous cells that are expressing these modified peptides. However, one anomaly of the tumour environment is its ability to be immunosuppressive: T-cells are inhibited and the tumour cells continue to grow and metastasise. Several mechanisms have been described by which tumours can suppress the immune system.

- Secretion of cytokines
- Alterations in antigen-presenting cell subsets
- Co-stimulatory and co-inhibitory molecule alterations
- Altered ratios of regulatory T-cells (Tregs) to effector T-cells

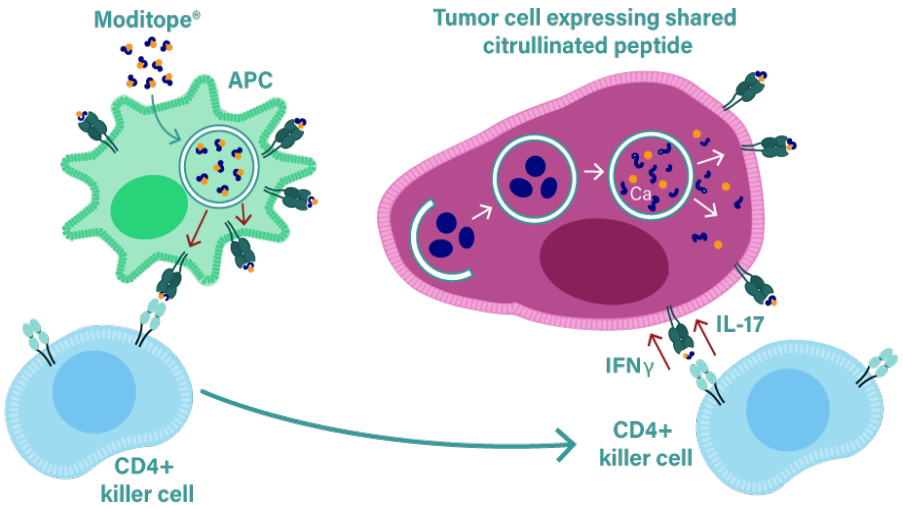
CD4 T-cells are the orchestrators of the immune response and, when activated within a tumour, release interferons (IFNs) that can reverse the immunosuppressive environment and can act directly to upregulate major histocompatibility complexes (MHC) presented by APC and stimulate the release of pro-inflammatory chemokines to promote further the immune response. The autophagy process activates a cascade of events that ultimately presents citrullinated peptides on MHC molecules, which will trigger the immune response.

Moditope technology

Moditope exploits the normal immune response to 'stressed' cells

Scancell has identified and patented a series of modified epitopes that stimulate the production of killer CD4+ T-cells that destroy tumours without toxicity. The Moditope immunotherapy platform is based on exploiting the normal immune response to stressed cells, which is largely mediated by CD4+ T-cells, and harnessing this mechanism to eradicate cancer cells.

Moditope – Mechanism of action



Source: Scancell

- Citrullinated tumour-associated peptides (Moditope) are injected
- Moditope is taken up by the antigen presenting cells (APC)
- APC present the peptides to CD4+ killer T-cells
- Primed CD4+ killer cells enter the bloodstream

- Stressed tumour cells undergo autophagy and express citrullinated peptides
- Primed $CD4^+$ killer T-cells destroy cancer cells expressing shared citrullinated peptides

Scancell's first target for Moditope is vimentin – a major cytoskeletal protein found in mesenchymal cells (cells that can differentiate into different cell types). Many epithelial tumours switch from expression of cytokeratin to vimentin during metastasis in a process known as epithelial mesenchymal transition; this change in phenotype enables the cell to become mobile and metastasise to new locations in the body.

In addition, Scancell identified another abundant cytoplasmic protein that is a major substrate for autophagy and is citrullinated during autophagy. α-enolase is a key glycolytic enzyme that catalyses the dehydration of 2-phosphoglycerate to phosphoenolpyruvate, in the last steps of the catabolic glycolytic pathway. This metalloenzyme is upregulated in many cancers including breast, ovarian, pancreatic ductal carcinoma, lung cancer and liver cancer, to provide energy for their rapid proliferation.

Modi-1

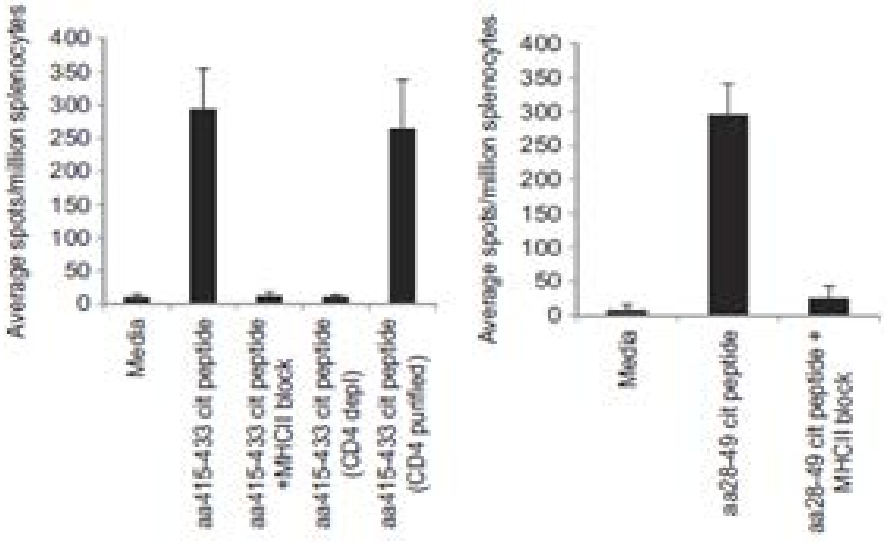
Modi-1 contains two citrullinated vimentin epitopes and one citrullinated epitope from α-enolase

Scancell's lead product, Modi-1 is a peptide therapeutic vaccine which contains a combination of two citrullinated vimentin peptides (Vim-1 and Vim-2) and one citrullinated α-enolase (Eno-1) epitope. These epitope targets are known to be highly expressed in triple negative breast cancer (90%), ovarian cancer (95%) and osteosarcoma (100%).

Citrullinated epitope-specific responses are CD4 mediated

Responses specific for citrullinated aa415-433 and aa28-49 peptides were shown to be CD4 mediated by depletion of CD4 cells before analysis or addition of MHC class II blocking antibody.

Citrullinated epitope-specific responses are CD4 mediated



CD4 mediated response induced by Cit 415-433

CD4 mediated response induced byCit 28-49

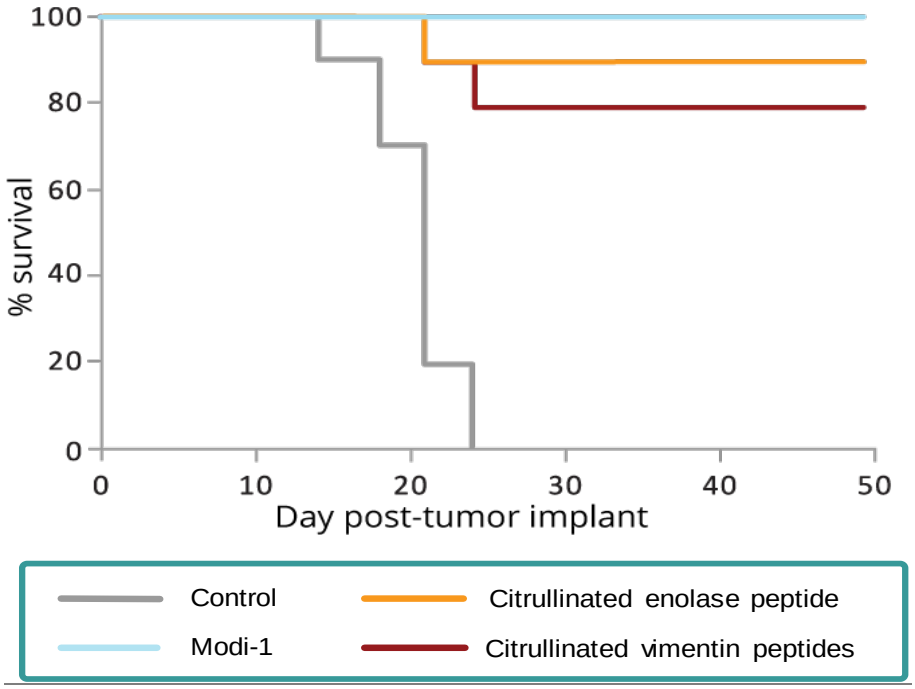
Source: Scancell

In vivo pre-clinical studies produced 100% survival rates

In vivo study

The following graph shows an *in vivo* study on tumour bearing mice (B16 expressing HLA-DR4 under the influence of a IFNg inducible promoter). The pre-clinical results with this aggressive tumour cell line show an excellent overall survival after 35 days after immunisation with citrullinated vimentins or citrullinated α-enolase with 80% survival and 90% survival, respectively after 38 days. The combination of the three citrullinated peptides that constitute Modi-1 brings an even greater effect as 100% of the mice survived after 38 days.

Moditope *in vivo* study



Source: Scancell

A single immunisation with citrullinated peptides from vimentin and α-enolase induced potent $CD4^+$ T-cells, potent anti-tumour activity and long term survival in 100% of animals with no associated toxicity.

These exciting results demonstrate how Modi-1 can mediate a potent anti-tumour response through a $CD4^+$ T-cells mediated against citrullinated epitopes on tumour cells. They also illustrate for the first time how citrullinated peptides produced during autophagy may offer attractive targets for cancer therapy.

Due to the reversal of the immunosuppressive tumour environment, there is no longer any need to add a checkpoint inhibitor, offering a completely new approach in immunotherapy.

Modi-1 proof-of-concept study to start in 2018

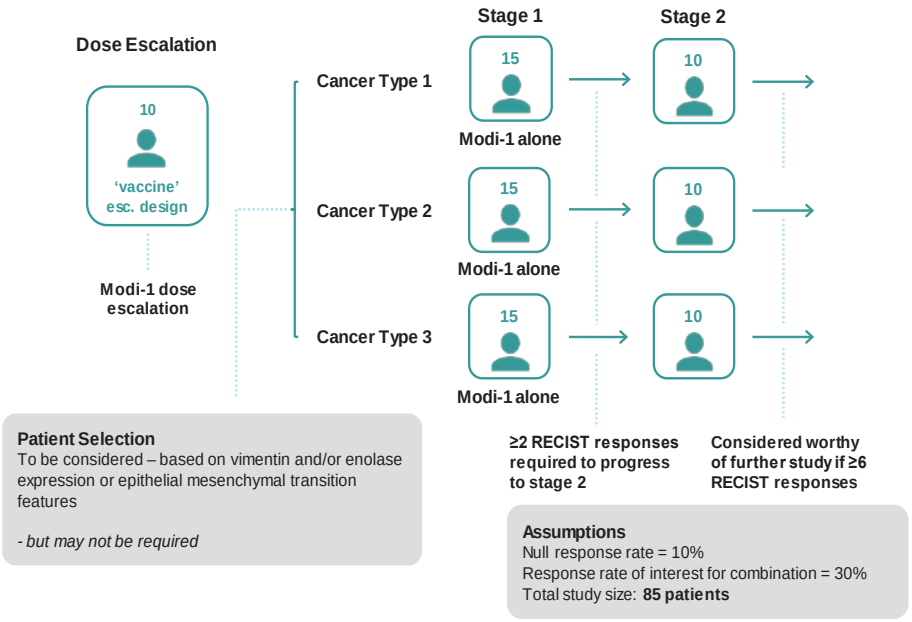
Modi-1 Clinical proof-of-concept as monotherapy

Scancell's lead product from this platform, Modi-1, is expected to enter a Phase I/IIa proof-of-concept monotherapy trial in 85 patients with advanced breast, ovarian cancer and osteosarcoma in 2018. The initial readout is expected during 2019.

- **Phase I:** Dose escalation in 10-20 patients to determine a dose that induces a cellular immune response
  - Alternative designs will be considered including single patient dose escalation

- **Phase IIa:** Extension/expansion of cohort from Phase I study
  - Primary objective: single agent objective response rate (ORR)
  - Secondary objective: safety of Modi-1
  - Two stage design requires 25 patients per cancer type to demonstrate an ORR of 30%

Design of planned Modi-1 phase I/IIa trial



Source: Scancell

R&D pipeline and IP

Pipeline and timetable

Scancell's two proprietary immunotherapy platforms are being developed in parallel through a pipeline of four products targeting cancers with unmet medical need.

Scancell – R&D pipeline

Platform	Product candidate	Indication	Pre-clinical	Phase I	Phase II	Phase III	Approved
ImmunoBody	SCIB1	Melanoma	→	→	→		
	SCIB2	Non-small cell lung cancer	→				
	SCIB1 PLUS	Melanoma	→				
Moditope	Modi-1	Triple –ve breast cancer Ovarian cancer Osteosarcoma	→				

Source: www.cancer.gov, Hardman & Co Life Sciences Research

The ImmunoBody platform comprises SCIB1 and SCIB1 PLUS for melanoma and SCIB2 for non-small cell lung (NSCL) cancer. Modi-1 belongs to the Moditope platform and is currently at the pre-clinical stage.

Scancell – Development schedule

Product candidate	Indication	2016	2017	2018	2019
SCIB1	Melanoma	GMP manufacture, IND		Ph II in combination with PD-1	
SCIB2	Non-small cell lung cancer	Cell banks, Feasibility	GMP manufacture, Toxicology	Ph I/II in combination with PD-1	
SCIB1 PLUS	Melanoma				
Modi-1	Triple –ve breast cancer Ovarian cancer Osteosarcoma		Feasibility, GMP manufacture, Toxicology	Ph I/II	

Source: Hardman & Co Life Sciences Research

Despite the fact that there will be no further patient enrollment in the first proof-of-concept SCIB1 trial in melanoma, existing patients will continue to be monitored to extend the unprecedented survival results seen to date. In addition, the next two years will be important for Scancell. First, it will initiate the Phase IIb clinical trial with SCIB1 in combination with an anti-PD-1 checkpoint inhibitor, led by Dr Keith Flaherty and in a number of renowned oncology centres such as Boston, Sloan Kettering, MD Anderson and University of Colorado. Secondly, Scancell will commence a Phase I/II proof-of-concept trial with Modi-1 in osteosarcoma, breast and ovarian cancer.

Further funds will be required to move programmes into the next stage

Further funds will be needed to extend Scancell's clinical programmes to the next stage which could come for an equity capital increase or by licensing out some of its assets (eg SCIB1 for melanoma), or a combination of both.

Collaborations

Scancell already has a number of existing collaborations in place.

Scancell – Current collaborations

Company	Theme	Date	Description
Merck KGaA	ImmunoBody	02/07/2009	Licensing agreement with Merck KGaA for two patents required for development and commercialisation of protein ImmunoBody vaccines. Under the agreement, Scancell has non-exclusive worldwide rights to use the two patents to further develop and commercialise ImmunoBody vaccines in all therapeutic areas
Ichor Medical Systems	Use of TriGrid delivery system	16/07/2009	Agreement with Ichor Medical Systems to use TriGrid electroporation device for the delivery of SCIB1
Cancer Research Technology	ImmunoBody	13/09/2013	Development of two ImmunoBody vaccines against Tie-2 and CD55 proteins for the treatment of solid tumours
ImmunID	ImmunoBody	30/07/2015	Use of ImmunID's proprietary product: ImmunTraCkeR as a clinical companion
Karolinska Institute	Citrullination	11/03/2016	Strategic collaboration to explore the role of citrullination in cancer
Eurogentec SA	GMP manufacture of SCIB1	22/07/2016	GMP manufacture of SCIB1 for future clinical trials

Source: Company announcements, Hardman & Co Life Sciences Research

Collaboration with Karolinska for further scientific evaluation of citrullination

Karolinska Institute

In March 2016, Scancell entered into a strategic collaboration with the Rheumatology Unit at the Karolinska Institute to further explore the role played by citrullinated proteins in the treatment of cancer. Professors Klareskog and Malmström from this unit have discovered that citrullinated proteins play a central role in the pathogenesis of autoimmune disease, including rheumatoid arthritis. This complements the finding by Scancell that citrullinated peptides are therapeutic targets for cancer, which is fundamental to their use in the Moditope immunotherapy platform.

Intellectual property

Scancell holds several patents to protect both its technology platforms. ImmunoBody and Moditope. The list of patents and the status are listed below.

Scancell – patent portfolio

Title	Publication no	Date	Status
Polypeptides capable of binding to CD64 and comprising one or more heterologous T-cells epitopes, and their uses	1354054	26/01/2001	Granted
Nucleic acid	2193803	28/03/2007	Granted in most countries
Anti-tumour responses to modified self-epitopes		07/08/2013	Under examination
Anti-tumour immune responses to citrullinated enolase		20/07/2015	UK, case filed

Source: Scancell, Hardman & Co Life Sciences Research

Commercial opportunity

Melanoma: SCIB1 market opportunity

Description

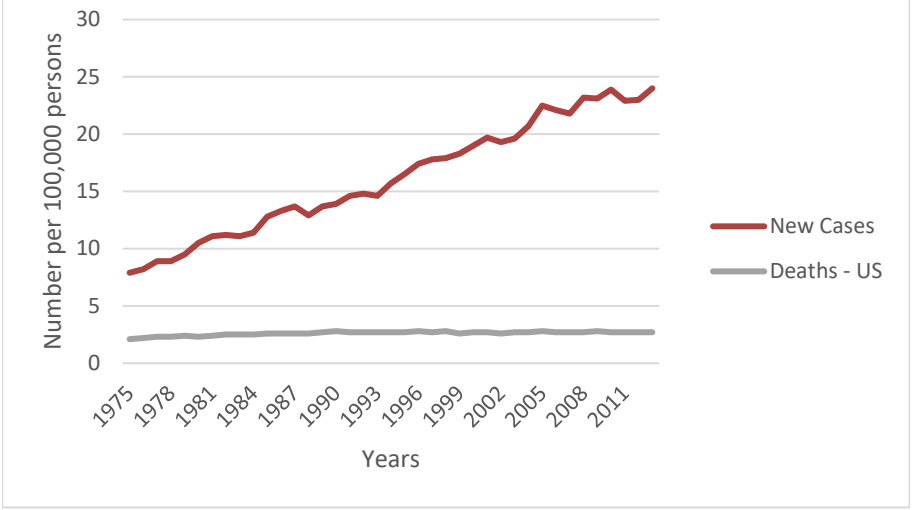
Melanoma is a type of skin cancer that often spreads to other organs in the body. The most common sign of melanoma is the change in an existing mole or the appearance of a new mole. The first-line of treatment is surgery but sometimes the melanoma cannot be removed completely as it has spread to other organs. Or, even when it is completely removed, it can sometimes return. There is still an unmet need to treat this relatively common type of cancer. Melanoma accounts for only less than 5% of skin cancer cases but causes a large majority of skin cancer deaths due to its propensity to spread to other parts of the body.

The American Cancer Society's estimates for melanoma in the US for 2016 are:

- 76,380 new melanomas will be diagnosed in the US (about 46,870 in men and 29,510 in women)
- About 50,000 new cases per annum in the EU
- 10,130 people are expected to die of melanoma in the US (about 6,750 men and 3,380 women) each year

The number of new cases of people affected by melanoma have been rising on average 1.4% each year over the last 10 years with the death rate being stable over that period. The increase is due to the aging population and the five years' survival is currently of 91.5%.

Number of melanoma cancer per 100,000 persons in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

Melanoma is sub-divided in four different stages, depending of the size of the cancerous area and whether it has spread to other parts of the body.

Melanoma 5 year survival rates			
Stage	**Incidence**	**5yr survival (Stage)**	**Description**
Stage I	67%	97% (A) 92% (B)	The melanoma is thin, <1mm thickness but might have broken the surface of the skin (ulcerated). It has not spread elsewhere and it is unlikely that the melanoma has grown deep enough into the skin
Stage II	19%	81% (A) 70% (B) 53% (C)	Melanomas will be thicker than 2mm and possibly ulcerated. Like stage 1, stage 2 melanomas will only be in the skin and there will be no indication of any spread to lymph nodes. However, stage 2 patients have a higher risk of the disease progression
Stage III	11%	78% (A) 59% (B) 40% (C)	Cancer cells have spread into skin, lymph vessels, or lymph glands close to the melanoma
Stage IV	1%	15-20%	Cancer has spread from where it started to another part of the body (lung, liver, bone, brain, lymph node, abdomen). Also termed advanced melanoma

Source: Cancer.org, Hardman & Co Life Sciences Research

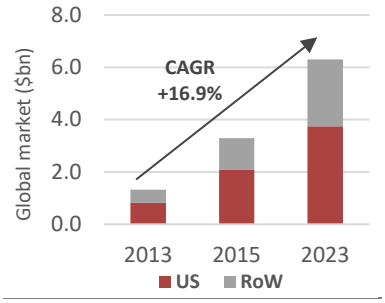
Depending on the stage of the cancer, four treatment options exist:

- Surgery for all stages of melanoma
- Radiation therapy
- Chemotherapy
- Immunotherapy – cytokines (Interferon, IL-2), TNFα, Ipilimumab, and PD-1's

Melanoma market

Globally, the metastatic melanoma market is projected to grow with a CAGR of 16.9% from $1.3bn in 2013 to $6.3bn by 2023. The US represents 60-64% of the global market during this period.

Global melanoma market



Source: Hardman & Co Life Sciences Researchl

In 2011, the launch of Yervoy onto the melanoma market positioned BMS as a key player in immuno-oncology. Yervoy targets CTLA-4 and has rapidly become the best-selling drug on the melanoma, with sales of $1.1bn in 2015. Cumulative sales since launch are $4.5bn. With the launch in 2014 of its second melanoma asset, the anti-PD-1 antibody, Opdivo (nivolumab) with cumulative sales of $480m to date, BMS is expected to strengthen further its position in the checkpoint immunotherapy and melanoma market. However, competition is intense with Keytruda (pembrolizumab, Merck & Co), also targeting PD-1, being approved by the FDA in 2014 and already achieving $621m cumulative sales, and now seeking first-line treatment approval.

Given that the overall response rate using checkpoint inhibitors is disappointing, only in the 20-40% range, there remains a significant opportunity to improve outcomes. Non-responders to immunotherapy have no further treatment options apart from the largely ineffective chemotherapy regimens. This represents the target population for SCIB1.

With 11 approved and well established drugs used currently in melanoma, and with more than 198 open studies registered[12], Scancell would be entering a crowded market place. However, good results in the combination study, backing up those obtained in the proof-of-concept trial, would be used to entice a licensing partner to take this asset to the next stage and commercialisation in melanoma.

[12] www.cancer.gov

Approved melanoma drugs				
Drug	**Name**	**Company**	**Mode of action**	**2015 sales**
Yervoy	Ipilimumab	BMS	CTLA-4 monoclonal antibody	$1,126m
Keytruda	Pembrolizumab	Organon	PD-1 humanised monoclonal antibody	$566m
Opdivo	Nivolumab	BMS/Ono	PD-1 humanised monoclonal antibody	$475m
Mekinist	Trametinib	Novartis	MEK kinase inhibitor	$453m
Tafinlar	Dabrafenib	Novartis	BRAF kinase inhibitor	$453m
Zelboraf	Vemurafenib	Roche/Genentech	BRAF kinase inhibitor	$222m
Cotellic	Cobimetinib	Exelixis/Roche	BRAF/MEK kinase inhibitor	$2m
Aldesleukin IL-2	Interleukin-2	generic	General immune system boost	N/A
DTIC-Dome	Dacarbazine	Bayer	DNA Alkylating agent	N/A
Imlygic (T-vec)	Talimogene Laherparepvec	Amgen	Oncolytic virus	N/A
Intron A	Recombinant Interferon alfa-2b	Merck & Co	General immune system boost	N/A

Source: Company reports; Hardman & Co Life Sciences Research

In October 2015, the FDA approved Imlygic (T-VEC, talimogene laherparepvec. Amgen), the first oncolytic virus therapy for the treatment of some patients with metastatic melanoma that cannot be removed surgically. Imlygic uses a modified version of the herpes virus to infect and break down cancer cells without harming normal cells. It is injected directly into tumours in the skin and lymph nodes. In addition to infecting and lysing cancer cells when injected directly, Imlygic induces responses in non-injected lesions, suggesting that it triggers an anti-tumor immune response similar to those of other anti-cancer vaccines.

SCIB1 is targeting part of the melanoma market worth $2.5-5.0bn

With SCIB1, Scancell is targeting the stage II/III melanoma market, which is thought to represent ~30% of melanoma patients. In 2013, there were an estimated 1,034,460 people living with melanoma just in the US[13] of which 220,000 may be suitable for adjuvant therapy (following resection of the tumour). Of these about 45% of patients would be suitable for SCIB1 treatment (HLA-A2 sub-type). Based on an estimated annual cost of $25,000-$50,000, this segment of the market alone would be worth $2.5-5.0bn.

The table below describes the treatment opportunity for SCIB1 in melanoma patients.

Scancell – SCIB1 in melanoma			
Stage	**Incidence**	**5 year survival**	**Description**
IA	67%	97%	Surgery
IB		92%	Surgery
IIA	19%	81%	Surgery + SCIB1
IIB		70%	Surgery + SCIB1
IIC		53%	Surgery + SCIB1
IIIA	11%	78%	Surgery + SCIB1
IIIB		59%	Surgery + SCIB1 + Checkpoint inhibitors, BRAF inhibitors
IIIC		40%	Surgery + SCIB1 + Checkpoint inhibitors, BRAF inhibitors
IV	1%	15-20%	Checkpoint inhibitors BRAF inhibitors T-Vec; CAR-T; TCR SCIB1 + checkpoint inhibitors

Source: Scancell, Hardman & Co Life Sciences Research

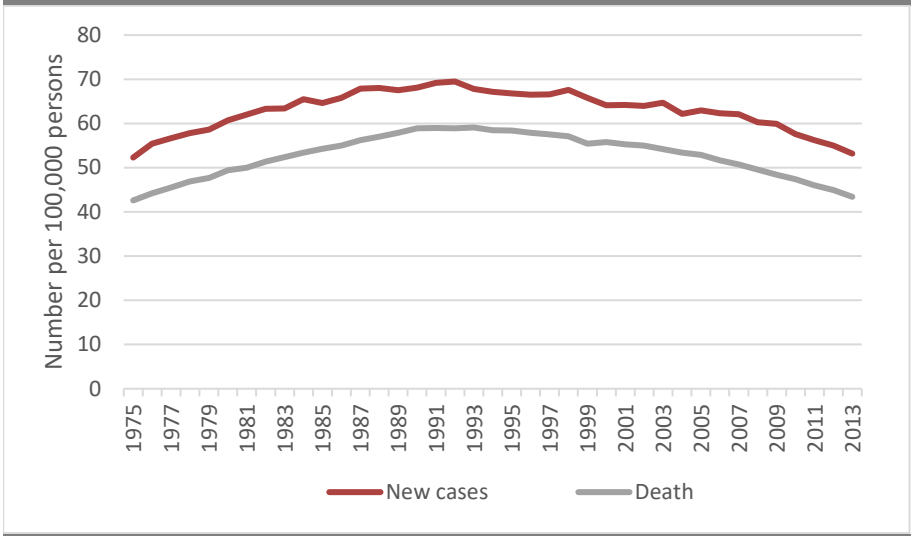
[13] American Cancer Society website

NSCL cancer: SCIB2 market opportunity

Presentation

Non-small cell lung cancer (NSCLC) accounts for over 85% of all lung cancers and is a leading cause of death. There are more than 220,000 new cases in the US annually and 150,000 deaths. This type of lung cancer occurs mainly in current, former or passive smokers. The graph below shows the number of new NSCLC cases per 100,000 of population. It demonstrates clearly the very poor prognosis of people with this condition with a five year survival rate of only 17.7%.

Number of NSCL cancer per 100,000 persons in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

Despite better understanding of lung cancer and the increased number of available drugs, the graph indicates that there has been little improvement in the survival rate from this type of cancer, with surgery remaining the only treatment option. The poor prognosis with NSCLC is often attributed to the fact that diagnosis is made only when the disease is well advanced.

Non-small cell lung cancer can be subdivided in 3 different types:

- **Adenocarcinoma** – Accounting for 40% of the lung cancer, adenocarcinoma has the characteristic to grow slower than other type of lung cancer and then tend to have a better prognosis. They are usually found in the outer part of the lung
- **Squamous cell carcinoma** – They are located inside the airways of the lung
- **Large cell carcinoma** – It can appear in any part of the lung and tends to grow and spread quickly

Depending on the stage of the cancer, five treatment options exist for people with NSCLC:

- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
- Radiofrequency therapy

NSCLC market

Hardman & Co estimates that the global market for NSCLC drugs treatment was ca.$7.0bn in 2015. Several forecasters suggest that the market looks set to grow 8-13% over the next five years to $11-12bn. Current standard of care is Avastin (used also in other conditions; Roche), which dominates the market with sales of ca.$7bn in 2015 and cumulative sales of $57.2bn since launch, together with an old drug, Taxotere (BMS).

The setback seen by BMS highlights the need for more efficacious therapies

The market for NSCLC drugs had been expected to grow substantially over the next five years following the launch of PD-L1 inhibitors. However, they received a significant setback recently, when Opdivo (BMS) was found to be no better that chemotherapy in a study of 541 treatment naïve patients newly diagnosed with advanced lung cancer (CheckMate -026; BMS website 5th August 2016). The study end-point was a delay in disease progression or death compared to chemotherapy. However, this goal was missed. The results were a surprise to the market because in a similarly designed study. Keytruda (Merck & Co) had previously been shown to delay disease progression in newly diagnosed drug naïve NSCLC patients.

10% share of the target NSCLC market would equate to sales of $1-2bn

These results, together with the high incidence and poor prognosis for NSCLC, demonstrate that it is a market of unmet need and with the very high death incidence, NSCL cancer market is desperately in need of a new and effective drug. In 2013, there were an estimated 416,000 people living with lung and bronchus cancer in the United States. If we consider SCIB2 to have the same annual cost (in the range of $25,000-$50,000), a 10% market share would bring a sales range of $1bn to $2bn for the US market only.

With 20 approved and well established drugs used currently in NSCLC and with more than 354 open studies registered,[14] SCIB2 would be entering an even more crowded market. Again, we are of the opinion that Scancell will likely out-license this asset for late-stage clinical trials and commercialisation.

Ranking of NSCL cancer approved drugs

Rank	Name	Drug	Company	MoA	2015 sales	Cumulative
1	Avastin	Bevacizumab	Roche	VEGF Recombinant human mAb	$6,948m	$57,205m
2	Alimta	Pemetrexed	Eli Lilly	Folate antimetabolite	$2,493m	$20,185m
3	Afinitor	Everolimus	Novartis	mTOR inhibitor	$1,607m	$6,045m
4	Tarceva	Erlotinib	Roche	EGFR kinase inhibitor	$1,228m	$12,343m
5	Abraxane	Paclitaxel	Abraxis/Celgene	Anti-mitotic	$968m	$3,349m
6	Iressa	Gefitinib	AstraZeneca	EGFR kinase inhibitor	$543m	$5,365m
7	Opdivo	Nivolumab	BMS	PD-1 humanised mAb	$475m	$481m
8	Xalkori	Crizotinib	Pfizer	ALK kinase inhibitor	$448m	$1,332m
9	Cyramza	Ramucirumab	Eli Lilly	VEGFR fully humanised mAb	$384m	$482m
10	Taxotere	Docetaxel	Sanofi	Anti-mitotic	$246m	$25,911m
11	Gemzar	Gemcitabine	Eli Lilly	Nucleoside analogue	$147m	$15,163m
12	Zykadia	Ceritinib	Novartis	ALK kinase inhibitor	$79m	$110m
	Tagrisso	Osimertinib	AstraZeneca	EGFR kinase inhibitor	$19m	$19m
	Portrazza	Nicitumumab	Lilly	EGFR Recombinant human mAb	Approved 2015	
	-	Methotrexate	Generic	Folate antimetabolite	Used since 1950	
	Alecensa	Alectinib	Roche	ALK kinase inhibitor	N/A	
	Gilotrif	Afatinib	B. Ingelheim	EGFR and HER2 kinase inhibitor	N/A	
	Paclitaxel	Taxol	Generic	Anti-mitotic	N/A	
	Paraplatin	Carboplatin	Generic	DNA-Alkylating agent	N/A	

Source: Hardman & Co Life Sciences Research

[14] www.cancer.gov

Moditope market opportunity

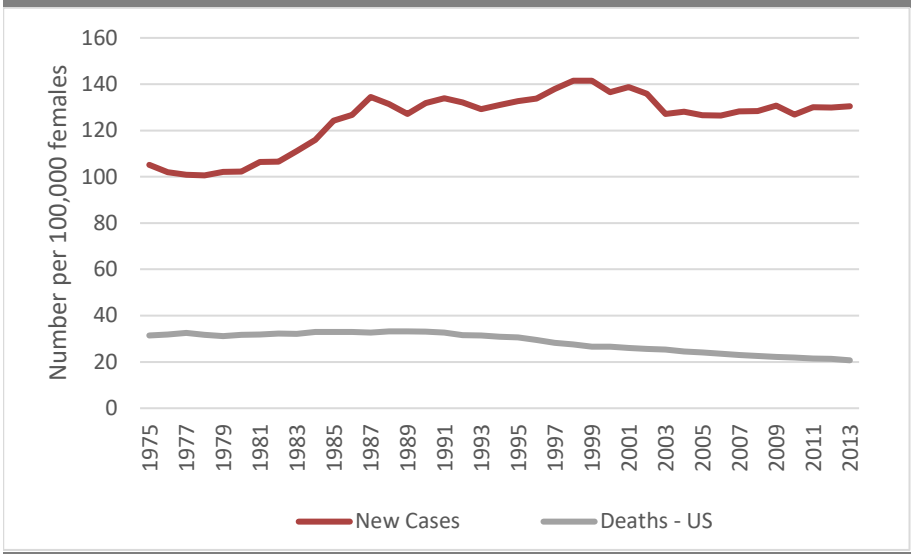
The Moditope market opportunity is more complex to measure as this immunotherapy has a completely different mechanism of action, targeting citrullinated proteins which are expressed in the majority of cancers. As such, this technology could be adapted to make multiple products across many hard-to-treat cancer indications.

Scancell is focusing its efforts and resources on triple negative breast cancer, advanced ovarian cancer and osteosarcoma. In osteosarcoma, Scancell would bring Moditope into orphan drug designation, and with it fast track regulatory review.

Triple negative breast cancer

Breast cancer is the number one cancer with more than 3m women affected in the US, in 2013 and with a five-year survival rate of 89.7%, benefiting from improved treatment regimens. The decrease in the death rate is believed to be a combination of early diagnosis through screening programmes, coupled with increased awareness and more efficacious drugs.

Breast cancer per 100,000 females in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

Breast cancer is classified in three categories:

- Hormone-receptor positive
- HER2 positive
- Triple negative

Triple negative breast cancer, the primary target for Modi-1, is where breast cancer cells do not have oestrogen or progesterone receptors and only low levels of HER2 – hence the term triple negative – which occurs in 15-20% of women with breast cancer. Consequently, any drugs that target specifically hormone or HER2 receptors will not work. Treatment protocols consist of a combination of surgery, radiation and chemotherapy (mainly doxorubicin, epirubicin, docetaxel and paclitaxel). Triple negative breast cancer tends to occur more often in younger women and is characterised by rapid growth and metastases.

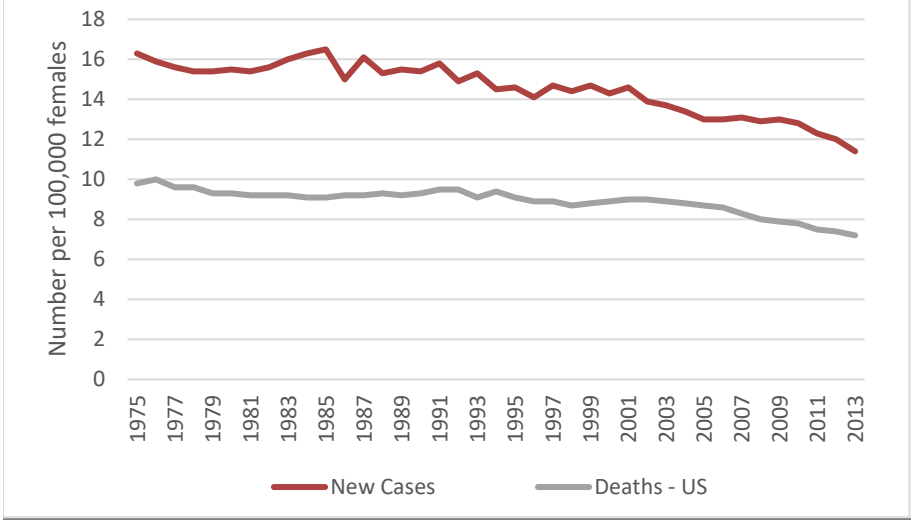
Advanced ovarian cancer

An advanced ovarian cancer is when the disease has reached stages II to IV:

- Stage II: the cancer has spread into the pelvis
- Stage III: the cancer has spread outside the pelvis to other part of the abdomen and/or nearby lymph nodes
- Stage IV: the cancer has spread beyond the abdomen to other parts of the body

In 2013, there were an estimated 196,000 women living with ovarian cancer in the US and 22,000 new cases are diagnosed every year. Amongst these patients, ca.70% will be in the advanced stage due to late diagnosis. Although there has been a reduction in incidence over time, it has been accompanied by a parallel reduction in deaths, leaving the five-year survival rate unchanged at 46.2%, highlighting the need for a new approach.

Number of ovarian cancer per 100,000 females in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

Treatments for advanced ovarian cancer consists of:

- Combination of chemotherapy and surgery (removal cancerous tissues)
- Targeted therapy with PARP inhibitor for certain patients with BRCA1 and BRCA2 mutations

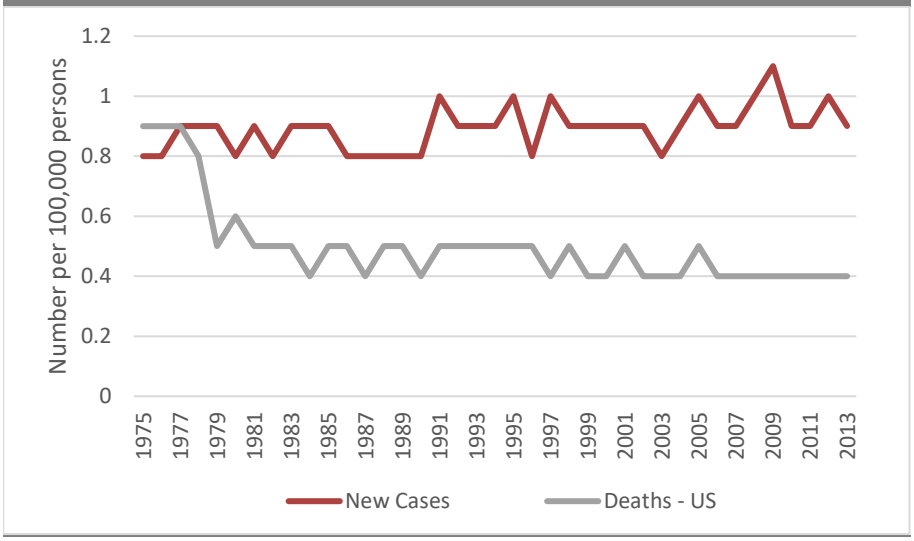
Osteosarcoma

Osteosarcoma is the most common type of bone cancer yet represents only 0.2% of all new cancer cases. Each year, about 800 new cases of osteosarcoma are diagnosed in the US and about half of these concern children and adolescents. Consequently, it would be described as uncommon and an orphan disease. The five year survival rate is 67.5%, little changed over time.

The types of treatment used for osteosarcoma include:

- **Surgery** – Limb-salvage surgery or amputation
- **Chemotherapy** – Usually, a combination of two or more drugs
- **Radiation therapy**

Bone cancer per 100,000 in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

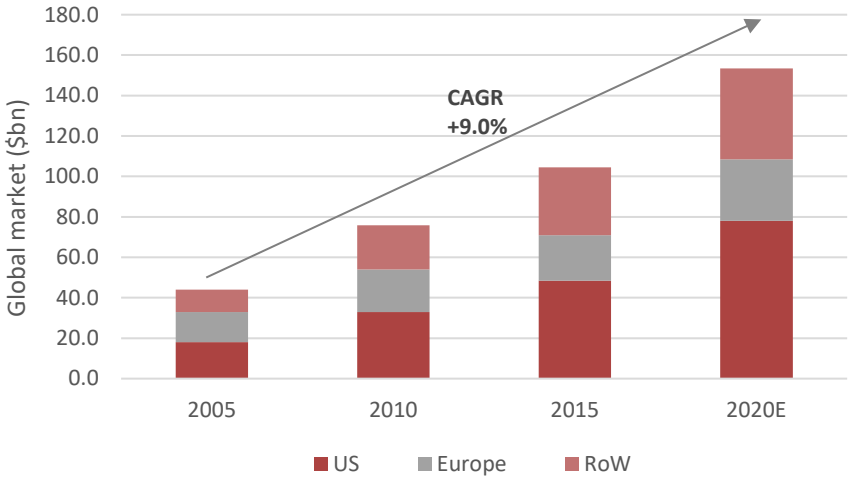
Oncology market

Global oncology drug market worth $105bn in 2015…

…and has +9.0% CAGR over last 10 years

Hardman & Co estimates that the global oncology market was worth $104.5bn in 2015 and represented +4.9% growth over 2014 in US$ terms, which suggests that the underlying growth rate was +8-9% in local currency terms. Our analysis is based on the ex-factory sales for the leading 110 branded drugs on the market, to which a figure representing the plethora of small/old/generic cancer drugs has been incorporated. Our data indicates that the global oncology market had +9.0% CAGR over the last 10 years.

Global oncology market

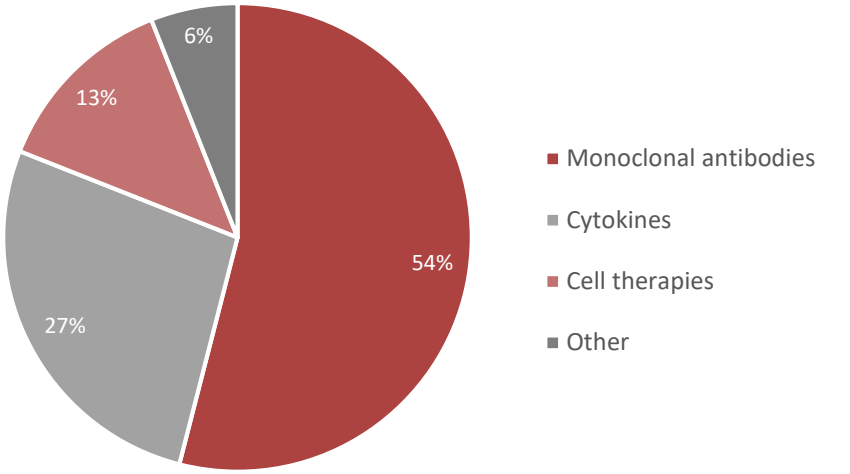


Source: Hardman & Co Life Sciences Research

Cancer drugs derived from antibodies represented 27% of the market last year

During the last decade, the global oncology market has been driven by sales of drugs derived from antibodies, which represented an estimated 27% of the market in 2015. Given the enormity of current development programmes for targeted immunotherapies, this status is unlikely to change in the next decade. This suggests that the historic growth rate of +8-9% compound will be maintained, such that Hardman & Co is forecasting the oncology market will grow to $154-161bn in 2020.

Immunotherapy programmes by technology



Source: Chang[15]; Hardman & Co Life Sciences Research

Scancell opportunity

Both of the Scancell immune-therapy platforms have the potential to reach sales >$1bn

Given that Scancell is developing two platform technologies that are sufficiently flexible and relatively easy to produce, and which can be applied to many different cancers, its products will become part of the overall immunotherapy segment of the market which is clearly a multi-billion dollar opportunity.

Competitive landscape

Despite the success, the demand for even more efficacious drugs is enormous

It is abundantly clear that an enormous number of companies, large and small, are researching new immunotherapies, which is currently one of the hottest fields in drug development. Much of this is being driven by the success of antibody-derived therapies for cancer treatment which recorded sales of just over $28.0bn in 2015. However, despite this obvious success, much more needs to be done. Even though many of these newer drugs are highly targeted, for a number of reasons they are proving less efficacious than had first been envisaged.

New technologies offer new approaches to overcome some of the problems observed clinically. In our opinion, the technologies fall into two categories:

- ***In-vivo*** – where the therapeutic is injected directly into the patient (and directly into the tumour in some cases)
- **Autologous** – where dendritic cells are removed, activated and then re-infused; personalised medicine

Both of Scancell's platform technologies are using the direct *in vivo* approach.

ImmunoBody is the only platform with a dual mechanism of action

There are several companies developing technologies that use a direct presentation *in vivo* approach. However, Scancell's ImmunoBody platform is the only approach that, in addition, has the facility for cross presentation, and it is this dual approach that generates potent higher avidity T-cell responses needed to fight cancer effectively.

[15] Chang, S. Global R&D is advancing the cancer immunotherapy field. 2015

CureVac uses similar approach…

…but based on RNA…

In terms of technology, CureVac has a similar approach to Scancell, with a direct presentation of the antigen, but based on an RNA vaccine instead of being DNA based. Inovio Pharma and Oncosec are considered also to be direct competitors of Scancell. However, in our opinion, these companies have developed proprietary electroporation administration techniques and then have searched for a suitable therapeutic vaccine with which they could use this method of administration. In contrast, Scancell has the proprietary and clever cancer immunotherapy platforms and can use any suitable electroporation method to administer the drug, i.e. it can simply buy-in the appropriate technology to overcome a problem – that of drug administration.

The majority of companies are using an autologous approach which, in our opinion, is much more complex and expensive to perform.

…the autologous approach is time-consuming and very expensive

Cancer immunotherapy development companies

Company	Approach	Technology
In vivo	**Direct or cross presentation**	
Advaxis	Attenuated *listeria* delivered bioengineered plasmids	*Lm*
Amgen	Engineered attenuated herpes simplex virus	T-VEC
Bavarian Nordic	Live virus vaccine platform	
CureVac	Viral-RNA vaccines	RNActive
Inovio Pharma	Viral DNA vaccine + Electroporation	SynCon
Oncosec Medical	Electroporation + DNA (IL-12) vaccine	ImmunoPulse
PsiOxus	'Armed' DNA vaccine	EnAd
Western Oncolytics	Viral derived technology delivering multiple immunotherapies in a single construct	WO-12
In vivo	**Direct and Cross presentation**	
Scancell	**DNA immunotherapy + electroporation (bought in)**	**ImmunoBody**
Scancell	**Peptide immunotherapy**	**Moditope**
Autologous	**Personalised approach**	
Adaptimmune	Autologous TCR vaccine	-
Asterias BioTher.	Autologous dendritic cell vaccine	AST-VAC1
BioNTech	Personalised mRNA vaccines	IVAC
Bluebird Bio	Autologous CAR-T-cell therapy	-
Cellectis	Autologous CAR-T-cell vaccine	TALEN
Dendreaon	Autologous dendritic cell vaccine	Provenge
Immunocore	Autologous CAR/TCR stimulation	ImmTAC
Juno Therapeutics	Autologous CAR-T-cell vaccine	-
Kite Pharma	Autologous CAR vaccine	eACT
NorthWest BioTher.	Autologous dendritic cell vaccine	DCVax
OSE Immunother.	Autologous CAR-T-cell vaccine	T-cellerator Memopi PENTRA

CAR = Chimeric antigen receptor; TCR = T-cell receptor; TAM = Tumour associated macrophages
This list is not comprehensive
Source: Hardman & Co Life Sciences Research

It should be noted that although we have endeavoured to be as thorough as possible in identifying the most relevant immuno-oncology companies working in the field that might compete with Scancell's technology, our list should not be considered comprehensive.

Financials & Investment case

Forecasts assume that Scancell raises $30m/£22m to fund the proposed clinical trial programme

Scancell raised £5.8m net of expenses in April 2016 to prepare the groundwork for the upcoming clinical trial programme – manufacturing of clinical trial materials, preparation of INDs etc – and for investment in corporate infrastructure. In order to actually undertake the first three planned clinical trials in the US and EU, Scancell will need an estimated $30m/£22m of new capital. Our forecasts assume that a capital raise of this order of magnitude is achieved by the end of fiscal 2017. In the event that a different level of funding is achieved, Scancell is likely, and able, to scale-down or scale-up its aspirations.

The financial statements of Scancell are straight-forward and dominated by three figures. First, the amount of cash being invested into R&D to fund the clinical trial programme; secondly, the ongoing SG&A costs to execute on the strategy; and thirdly, the R&D tax credits from the UK government. These, in turn, drive the cashflow and determine the point at which management needs to raise more capital.

Profit & Loss

Our forecasts assume that Scancell will invest ca.£25m/$34m in its clinical trial programme, spread over four financial years. The investment in corporate overhead (SG&A) is dependent on fully executing the three trial programme and the R&D spend will be biased towards trial completion – 40% up-front/60% on completion.

Profit & Loss account

Year end April (£m)	2014	2015	2016	2017E	2018E	2019E
Sales	0.00	0.00	0.00	0.00	0.00	0.00
SG&A	-0.77	-0.75	-1.00	-2.35	-2.58	-2.84
R&D	-1.68	-2.12	-2.01	-3.62	-6.00	-9.70
EBITDA	-2.41	-2.84	-2.99	-5.94	-8.56	-12.52
Depreciation & Amortis	-0.04	-0.03	-0.02	-0.02	-0.02	-0.02
Licensing/Royalties	0.00	0.00	0.00	0.00	0.00	0.00
Underlying EBIT	**-2.45**	**-2.87**	**-3.01**	**-5.96**	**-8.58**	**-12.54**
Share based costs	-0.05	-0.09	-0.04	-0.04	-0.05	-0.06
Exceptional items	0.00	0.00	0.00	0.00	0.00	0.00
Statutory EBIT	-2.50	-2.96	-3.04	-6.01	-8.63	-12.60
Net financial income	0.03	0.13	0.01	0.01	0.11	0.06
U/lying pre-tax profit	**-2.42**	**-2.74**	**-2.99**	**-5.96**	**-8.47**	**-12.49**
Reported pre-tax	-2.47	-2.83	-3.03	-6.00	-8.52	-12.54
Reported taxation	0.25	0.41	0.45	0.72	1.20	1.94
Tax rate	-10%	-15%	-15%	-12%	-14%	-15%
Underlying net income	**-2.18**	**-2.32**	**-2.55**	**-5.23**	**-7.27**	**-10.55**
Statutory net income	-2.22	-2.41	-2.58	-5.28	-7.32	-10.60
Period-end shares (m)	224.95	224.95	261.56	411.66	411.76	411.86
Weighted average (m)	216.70	224.95	227.56	261.56	411.66	411.76
Fully diluted shares (m)	216.70	240.48	249.23	254.84	291.54	441.64
Underlying Basic EPS (p)	**-1.00**	**-1.03**	**-1.12**	**-2.00**	**-1.77**	**-2.56**
Statutory Basic EPS (p)	-1.03	-1.07	-1.14	-2.02	-1.78	-2.57
U/l Fully-diluted EPS (p)	**-1.00**	**-0.93**	**-1.00**	**-1.79**	**-1.65**	**-2.39**
Fully-diluted EPS (p)	-1.03	-0.97	-1.01	-1.81	-1.66	-2.40
DPS (p)	0.00	0.00	0.00	0.00	0.00	0.00

Source: Hardman & Co Life Sciences Research

Balance sheet

- **2016 fund raise** – Scancell raised £5.8m net of expenses in April 2016 through a Placing and Open offer
- **Net cash** – At 30th April 2016, the net cash position was £6.5m which is being used to prepare the groundwork for the next wave of clinical trials
- **Clinical trial programmes** – The cost of undertaking the planned three trial programmes in the US and EU is estimated to be about $30m, with the majority being spent in the US
- **Capital raise** – Forecasts are based on $30m/£23m being raised from markets by the end of fiscal 2017

Balance sheet

@ 30th April (£m)	2014	2015	2016	2017E	2018E	2019E
Shareholders' funds	9.08	6.75	9.99	26.42	19.10	8.50
Share capital	0.22	0.22	0.26	0.40	0.40	0.40
Reserves	8.85	6.53	9.73	26.02	18.70	8.10
Short-term loans	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash & secs.	5.57	3.06	6.53	22.72	14.99	3.72
Invested capital	**3.51**	**3.70**	**3.46**	**3.69**	**4.11**	**4.78**
Fixed assets	0.12	0.09	0.06	0.04	0.02	0.02
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Trade debtors	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
Other debtors	*0.15*	*0.14*	*0.12*	*0.12*	*0.12*	*0.10*
Tax credit/(liability)	*0.37*	*0.66*	*0.44*	*0.72*	*1.20*	*1.94*
Trade creditors	*-0.23*	*-0.37*	*-0.32*	*-0.34*	*-0.39*	*-0.44*
Other creditors	*-0.31*	*-0.23*	*-0.45*	*-0.26*	*-0.26*	*-0.26*
Debtors less creditors	-0.02	0.19	-0.01	0.24	0.67	1.34
Invested capital	**3.51**	**3.70**	**3.46**	**3.69**	**4.11**	**4.78**
Net cash/(debt)	**5.57**	**3.06**	**6.53**	**22.72**	**14.99**	**3.72**

Source: Hardman & Co Life Sciences Research

Cashflow

- Cashflow is dependent largely on the investment in R&D and SG&A, offset by R&D tax credits, flowing through from the P&L account
- **Cap-ex** – Given that most activities are out-sourced, the company has minimal capital expenditure requirement. In the next two years, a modest level of cap-ex might be required to fund the new US office and the clinical trial co-ordination centre in Oxford
- **Tax credits** – There is usually a timing difference between R&D investment and the cash rebate receivable from HMRC
- **Capital increase** – As stated above, we have incorporated a capital increase of $30m/£22m (gross) into our forecasts for fiscal 2017

Cashflow						
Year end April (£m)	**2014**	**2015**	**2016**	**2017E**	**2018E**	**2019E**
Trading profit	-2.45	-2.87	-3.01	-5.96	-8.58	-12.54
Depreciation	0.04	0.03	0.02	0.01	0.01	0.00
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Working capital	0.19	0.08	-0.02	-0.01	-0.01	-0.01
Other	0.00	0.00	0.00	0.00	0.00	0.00
Company op cashflow	**-2.22**	**-2.76**	**-3.00**	**-5.96**	**-8.58**	**-12.55**
Net interest	0.02	0.02	0.00	0.01	0.14	0.09
Tax	0.13	0.12	0.67	0.45	0.72	1.20
Free cashflow	**-2.10**	**-2.62**	**-2.33**	**-5.51**	**-7.72**	**-11.26**
Dividends	0.00	0.00	0.00	0.00	0.00	0.00
Acquisitions	0.00	0.00	0.00	0.00	0.00	0.00
Disposals	0.00	0.00	0.00	0.00	0.00	0.00
Cashflow after invests.	**-2.09**	**-2.51**	**-2.32**	**-5.51**	**-7.72**	**-11.26**
Share issues	6.16	0.00	5.79	21.69	0.00	0.00
Change in net debt	**4.07**	**-2.51**	**3.47**	**16.18**	**-7.72**	**-11.26**
Hardman FCF/share (p)	-1.0	-1.2	-1.0	-2.1	-1.9	-2.7
Opening net cash	1.49	5.57	3.06	6.53	22.71	14.99
Closing net cash	5.57	3.06	6.53	22.71	14.99	3.73

Source: Hardman & Co Life Sciences Research

Valuation

Discounted cashflow

DCF is not appropriate at this stage

The best approach to valuing biopharmaceutical companies is to prepare detailed discounted cashflow analyses of key products through to patent expiry, and then to risk-adjust the NPV based upon industry standards for the probability of the product reaching the market. However, in the case of Scancell, the assets are considered to be at too early a stage with no stated commercial strategy – assets will probably be licensed out to big pharma for commercialisation – to undertake a reliable DCF valuation, without exhaustive analysis of the market opportunities, penetration rates and potential milestones and royalty payments.

Scancell's proprietary technologies are targeting a 'hot' field…

…attracting the major players…

Suffice to say, Scancell's proprietary technologies are in a 'hot' area and are targeting markets of significant unmet medical need. Products that have achieved a successful regulatory outcome and been commercialised have all seen rapid update and generated $1bn+ sales, which suggests that these flexible assets will be very attractive to big pharma and/or biotech companies. To that extent, it is probably more relevant to look at what large pharma is prepared to pay to gain access to such technologies.

Comparative valuation – M&A

…willing to pay handsome prices for the right assets

Another way of determining valuation looks at the prices that acquirers have been prepared to pay for the novel technology and assets. What is popping out from the table below is the ca.$1,000m deal that Bavarian Nordic signed with BMS in March 2015 for the rights to license and commercialise PROSTVAC, which is in phase III development for the treatment of asymptomatic or minimally symptomatic metastatic castration resistant prostate cancer. BMS paid $60m upfront payment with potential regulatory, sales and development milestones of $915m.

Deal comparators – Cancer vaccine assets

Licensor	Licensee	Type of deal	Stage of development	Date	Upfront ($m)	Milestones ($m)	Milestones
Bayer	Compugen	License	Pre-clinical	Aug-13	10	530	$530m ($30m preclinical activities, $500m potential milestone payment and high single-digit royalties)
Roche	Immatic	Collaboration	Pre-clinical	Nov-13	17	Undisclosed	Undisclosed, plus royalties
Boehringer Ingelheim	CureVac	License	Pre-clinical	Sep-14	45	550	$550m (for sales plus royalties)
Bristol-Myers Squibb	Bavarian Nordic	License	Phase III	Mar-15	60	915	$915m ($80m if exercised, $110m for regulatory, $230m development milestones, up to $495m in sales and double-digit royalties
MedImmune	Inovio	Licence	Phase I/II	Aug-15	27.5	700	$700m (development and commercial milestones, plus double-digit royalties)
Agenus	PhosImmune	Acquisition	Pre-clinical	Dec-15	9.9	35	$35m on achievement of certain milestones
AstraZeneca	Moderna Therapeutics	Collaboration	Pre-clinical	Jan-16 + Aug-16	-		Co-development agreement for selected oncology targets + $140m investment in Moderna
Merck & Co	Moderna Therapeutic	Collaboration	Pre-clinical	Jun-16	200	Undisclosed	Undisclosed, plus royalties
Roche	BioNTech	Global collaboration	Pre-clinical	Sept-16	310	Undisclosed	Upfront includes some near-term milestones Co-development & profit sharing elements

Source: Hardman & Co Life Sciences Research

Companies are willing to pay $10m to $45m for pre-clinical assets followed by big milestone payments if successful, with high single digit to double digit royalties.

Cancer vaccine research, with the use of the checkpoint inhibitors, is a hot area of development. Several companies have clinical development pipelines using more complex techniques compared to the flexibility of Scancell's platforms.

Roche pays BioNTech an upfront of $310m to gain access to novel mRNA vaccine platform

At the time of going to press, Roche, through its wholly-owned subsidiary Genentech, announced a global collaboration deal with BioNTech, whereby Genentech's immunotherapy portfolio would be combined with BioNTech's proprietary messenger RNA cancer vaccine platform to create tailored (personalised) immunotherapies for a number of cancer types. The upfront payment including some, clearly achievable, near-term royalties was stated to be $310m. Both companies will share the development costs along with a longer-term profit-sharing arrangement. This deal again highlights the high prices that major pharmaceutical companies are willing to pay to gain access to new technologies.

AZN recently increased its stake in Moderna

AstraZeneca originally agreed a collaboration with Moderna Therapeutics in 2013 to discover, develop and commercialise mRNA therapeutics for the treatment of cardiovascular, metabolic and renal diseases and some selected targets in oncology. This collaboration was extended in January 2016 through a new collaborative agreement for two specific pre-clinical immune-oncology programmes. Details of the financial terms were not disclosed. However, in August 2016, AZN did participate in a preferred stock placing undertaken by Moderna, investing $140m which equated to a 9% holding in the fully diluted share capital.

Merck & Co also signed collaboration deal with Moderna…

…for mRNA cancer vaccine…

…with a $200m upfront payment

In June 2016, Moderna also agreed a collaboration agreement with Merck & Co for a pre-clinical stage mRNA vaccine, which included a $200m upfront. Both companies will share the development costs for an mRNA-based personalised cancer vaccine which is expected to enter the clinic next year. Merck has the option, after human proof-of-concept data, to make an additional undisclosed payment to Moderna. Upon that exercise, the pair will equally split costs and profits under a worldwide collaboration arrangement, whilst retains the right to co-promote the vaccines in the US. The mRNA vaccine technology encodes a patient's specific neoantigens, unique mutations present in a specific tumour, and is intended to elicit a specific immune response to destroy those cancer cells. The program will focus on several types of cancer and the vaccines are expected to be synergistic with checkpoint inhibitors, such as Keytruda, Merck's anti-PD-1.

Comparative valuation – peer analysis

The enterprise value of Scancell does not reflect properly either the achievement or the IP position…

Scancell is trading on an enterprise value of £33m compared to a cumulative investment of £19m in R&D to get the company where it is today. Whether this is a true reflection of valuation is difficult to say.

…the EV of Inovio is 13.1x greater…

…with its main asset being the administration technology

Inovio has a diverse pipeline with several products in development including HIV, Hepatitis B and C, as well as universal influenza, vaccines, but only one of these is currently in clinical development (Phase II). Inovio has developed its own DNA plasmid cancer immunotherapy (SynCon) on which there is little clinical data available. The vaccine is administered via Inovio's own proprietary electroporation administration technology for which it has managed also to sign a number of licensing deals. In contrast, Scancell has developed two proprietary immunotherapy platforms and has the freedom to choose which electroporation technology to use to administer its products. In our opinion there is much greater value in the immunotherapy platform than in the delivery technology. Despite this, Inovio trades on an enterprise value 13.1x greater than that for Scancell.

The following table shows the comparative data for a group of relevant quoted peer companies. It is clear from the table that the markets put far greater value on companies that have validated technology, as evidenced by the signing of licensing deals. Looking at this data in its entirety suggests that there is considerable upside potential for Scancell.

Peer group valuations

Company	Advaxis	Bavarian Nordic	Galena Biopharma	Inovio	OncoSec	OSE Immuno	Scancell
	ADXS	BAVA	GALE	INO	ONCS	OSE	SCLP
Local currency	$	NKR	$	$	$	€	£
Share price	10.5	257.0	0.36	9.2	1.73	6.4	14.6
Shares in issue (m)	39.8	30.9	214.0	73.5	17.6	14.3	261.6
Market cap (lc)	418.4	7,950.1	77.0	673.0	30.5	91.2	38.2
Mkt cap (£m)	321.8	736.8	59.3	517.7	23.5	78.4	38.2
Cash	78.7	1,502.0	44.0	134.6	24.1	25.3	6.5
Debt	0.4	0.0	23.2	0.0	3.2	0.0	0.0
EV (lc)	339.2	6,448.1	9.9	538.4	3.2	65.9	31.7
EV (£m)	**261.0**	**597.6**	**7.6**	**414.1**	**2.5**	**56.6**	**31.7**
Relative EV	8.2x	18.9x	0.2x	13.1x	0.1x	1.8x	-
I-O stage of development	Phases I/II/III	Phases I/II/III	Phases II/III	Phases I/II	Phase II	Phase III	Phases I/II
Licensing deals	3	3	11	9	0	1	0

Prices taken at close of business on 21st September 2016
Source: Hardman & Co Life Sciences Research

Company matters

Registration

Incorporated in the UK with company registration number: 06564638

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Board of Directors

Board of Directors				
Position	**Name**	**Nominations**	**Remuneration**	**Audit**
Executive Chairman	Dr John Chiplin			
Chief Executive Officer	Dr Richard Goodfellow			
Chief Scientific Officer	Prof Lindy Durrant			
Development Director	Dr Sally Adams			
Non-executive director	Dr Matthew Frohn		M	C
Non-executive director	Dr Alan Lewis			
Non-executive director	Kate Cornish-Bowden		C	M

M = member; C = chair
Source: Company reports

Dr John Chiplin – Executive Chairman

John is based in San Diego and provides significant international experience in the US life science and technology industries. Most recently, John was instrumental in the NASDAQ Initial Public Offering of Benitec Biopharma (ASX: BLT; NASDAQ BNTC), the clinical stage biotechnology company, where he has been a Non-Executive Director since 2010. He also serves on the boards of Cynata Therapeutics, Adalta, Batu Biologics, Prophecy, ScienceMedia and the Coma Research Institute. Previously John was President and Chief Executive Officer of Polynoma, a Phase III cancer vaccine company, and from 2006 to 2009 he was Chief Executive Officer of Arana Therapeutics. Prior to this, was head of the ITI Life Sciences investment fund in the UK, where he managed significant negotiations regarding funding with Government Ministers.

Dr Richard Goodfellow – Chief Executive Officer

Dr Richard Goodfellow has over 25 years' experience in the pharmaceutical industry, both in multinational drug companies and smaller entrepreneurial biopharma companies. During his time at Astra, he oversaw the launch of Losec and other key products internationally. Thereafter, he held the post of Director of Licensing and New Business Development at Scotia Pharmaceuticals, where he was involved with the company's flotation on the London Stock Exchange. Dr Goodfellow is also a founder of Paradigm Therapeutics, a Cambridge based functional genomics company and is a former Director of Enact Pharma plc.

Prof Lindy Durrant – Chief Scientific Officer

Professor Lindy Durrant is an internationally recognised immunologist in the field of tumour therapy, Prof. Durrant has worked for over 20 years in translational research, developing products for clinical trials including monoclonal antibodies for diagnostic imaging and therapy and cancer vaccines. She has a personal Chair in Cancer Immunotherapy at the Department of Clinical Oncology at the University of Nottingham.

Dr Sally Adams – Development Director

Sally was Head of Neurology & Virology at British Biotech and Development Director at Neures Limited before becoming an independent consultant providing drug development and management services in biotechnology and pharmaceutical, specialising in biological entities. She has worked on many complex projects over the past 25 years including anti-infective vaccines, cancer immunotherapies and an innovative stem cell treatment for visual dysfunction. Sally previously worked as a development consultant to Scancell, providing guidance on the development of SCIB1, before her appointment as Development Director in May 2014.

Dr Alan Lewis – Non-Executive Director

Extensive experience in the pharmaceutical industry holding senior management positions at both major drug companies and early stage start-ups. He brings a proven track record in advancing drug R&D programmes and in raising capital. At Medistem he oversaw the acquisition by Intrexon in 2014 for $26m; at Novocell the $25.4m fund-raise and responsibility for a multi-year drug discovery collaboration with Pfizer; at Signal Therapeutics alliances with several drug companies prior to its $275m acquisition by Celgene. BSc I Physiology and Biochemistry from Southampton University and PhD in Pharmacology from University of Wales.

Dr Matthew Frohn – Non-Executive Director

Matthew started his career as a clinical and research scientist before moving into venture capital in 1999. He originally joined Oxford Technology making seed investments into start-up and early stage technology companies, predominantly in healthcare. More recently, he co-founded Longwall Venture Partners, an early-stage technology investment company with £70m under management. Matthew has a DPhil in Biochemistry from the University of Oxford.

Kate Cornish-Bowden – Non-Executive Director

Kate is a Chartered Financial Analyst and holds a Masters in Business Administration. She was executive director and senior portfolio manager at Morgan Stanley Investment Management's Global Core Equity Team prior to becoming its managing director. More recently, Kate has acted as a consultant providing financial research to private equity and financial training firms and was appointed a director of Investec Structured Products Calculus VCT plc in February 2011.

Facilities

Scancell's main laboratory is based in the department of Clinical Oncology in Nottingham, UK employing a total of 9 staff. Earlier in 2016, Scancell announced the opening of new offices in San Diego, California to support its ambitious US growth plans. From here it will coordinate the future Phase IIb clinical trials the company intends to run in the US for SCIB1 and facilitate discussions with the FDA. In addition, Scancell has also established a new base in the Oxford area for its UK corporate and development activities.

Capital increases

Since its Listing on PLUS in 2008, Scancell has raised just under £19m of capital in order to get the company and its assets to where they are today. The cash balance at the end of April 2016 was £6.5m, which will be sufficient to undertake the planning stages for the proposed clinical trial programme. Further capital, estimated at $33m/£23m will be required to fund these trials.

Comparative valuation

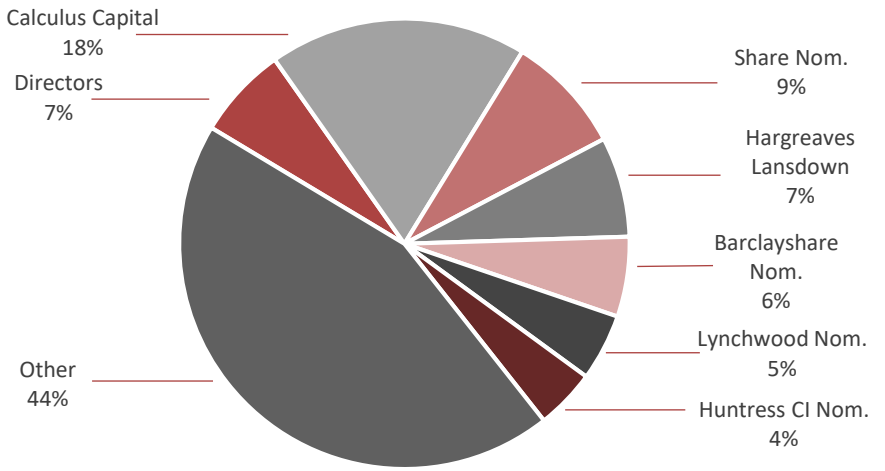
Comment	Date	Shares (m)	Price (p)	Raised (£m)	Shares o/s (m)	Valuation (£m)
Prior to flotation on PLUS				4.68	76.0	
Flotation on PLUS; Placing at 6.0p	Sep-08	26.0	6.0	1.56	102.0	6.12
Placing @ 6.0p	Dec-08	0.7	6.0	0.04	102.8	6.17
Open offer at 4.5p per share	Mar-10	51.4	4.5	2.31	154.1	6.94
Placing at 4.5p per share	Apr-10	4.6	4.5	0.21	158.7	7.14
Placing @ 4.5p	May-10	0.5	4.5	0.02	159.3	7.17
Issue new ordinary shares @ 9.55p	Jan-11	0.3	9.6	0.02	159.5	15.23
Subdivision of 1p shrs. into new 0.1p shares	Jun-11	0.0	0.0	0.00	159.5	15.23
Placing @ 5.0p	Jun-11	34.6	5.0	1.73	194.1	9.70
Issued to Scancell Ltd shareholders	Jul-13	20.0	22.5	0.00	214.1	48.12
Open offer @ 22.5p (1-for-22)	Jul-13	8.9	22.5	2.00	223.4	50.26
Exercise of option (Ichor)	Nov-13	1.6	4.5	0.07	225.0	0.00
Placing @ 17p	Mar-16	20.0	17.0	3.40	245.0	41.61
Open offer @ 17p (1-for-10)	Apr-16	16.6	17.0	2.82	261.6	44.46
	Total			**18.87**		

Prior to June 2011, the number of and share prices have been corrected for the 100-for-1 subdivision
Source: Hardman & Co Life Sciences Research

Share capital

The company has 261,558,099 Ordinary shares of 0.1p nominal value in issue. There are currently 27.3 million options outstanding, or 9.4% of the fully diluted share capital.

Major shareholders



Source: Company reports

Risks

Background

Investments in small early-stage pharmaceutical companies carry a significant risk and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cash flow breakeven and profitability.

Financial/Dilution risk

The company has sufficient cash to fund the preparative work needed for its clinical development programme. However, it will require $30m/£22m of new capital in order to undertake the planned trials. There is no guarantee that the company will be successful in raising such funds, nor on the terms that such capital is raised, which could be dilutive to shareholders.

Commercialisation

Management has not stated its plans for commercialisation. For large scale clinical trials and commercialisation of its assets the company is likely to seek a partner through an out-licensing arrangement. There is no guarantee that this would be on terms that are beneficial to shareholders.

Patent robustness

As with all IP-rich companies, there is risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. Any litigation could involve significant costs and uncertainties.

Regulatory

It is important for companies to liaise with regulators on a regular basis throughout the development programme. Any inadequacies could lead to regulatory action such as cessation of product development and loss of manufacturing or product licences.

Share liquidity

As with many small cap companies listed on AIM, there can be difficulty in buying and selling shares in volume. Market makers only guarantee prices in a very small number of shares.

Competition

The Company operates in a market dominated by larger multinational competitors, most of which have significant financial resources to fund development programmes, marketing activities, etc.

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www.fightcancerwithimmunotherapy.com

www.inovio.com

www.scancell.co.uk

www.wormbook.org/chapters/www_autophagy

www.cancer.gov

Glossary

Antibody	A large protein secreted by B-cells that binds to specific antigens. Antibodies help to destroy foreign entities or abnormal cells
Antigen	A substance that has the potential to cause the body to mount an immune response against it. It helps the immune system to determine whether something is self or non-self (foreign). Non-self antigens are recognised by the immune system as a threat and will trigger the immune response
APC	Antigen-presenting cell
Avidity	Accumulated strength of multiple affinities of individual non-covalent binding interactions, e.g. between a protein receptor and its ligand, and is commonly referred to as functional affinity. Avidity is distinct from affinity, which describes the strength of a single binding interaction
CTL	Cytotoxic T lymphocytes
Cytotoxic T-cells	Also called killer T-cells. They attack infected or abnormal cells by releasing toxic chemicals or by prompting the cells to self-destruct (apoptosis)
Epitope	The part of the antigen that is recognized by the immune system
HLA	Human leukocyte antigen
IFN	Interferon
IND	Investigational new drug
Leukocytes	Also called white blood cells. They provide a non-specific level of immune response. They play the main role in immune responses by protecting the body against diseases caused by microbes and abnormal cells. Some types of leukocytes patrol the circulatory system, seeking foreign invaders and diseased, damaged, or dead cells.
Lymphocytes	Mainly represented by the B-cells and T-cells. They provide a targeted protection against specific threats, whether from a specific microbe or a diseased or abnormal cell
MHC	Major histocompatibility complex – set of cell surface proteins essential for the immune system to recognize foreign molecules
ORR	Objective response rate
PAP	Prostatic acid phosphatase

Notes

Notes

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